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Instrumental variables (IV) techniques were used to estimate outcome differences between treatment options among marginal patients with early stage prostate cancer diagnosed during 1986-1993. Access to care, area socioeconomic and healthcare market characteristics affected choice of treatment and these associations varied among age groups. Unbiased estimates of treatment effects also varied among these age groups. Results suggest that an increase in aggressive treatment for patients with presumed localized early stage prostate cancer would have resulted in increased survival rates but these effects decreased with patient age. Further, an increase in surgery among those patients aggressively treated would have also increased survival and these effects increased with patient age. Health policy should be tailored to these differences between age subgroups of older men. Though results suggested that increased aggressive treatment in general, and surgery in particular, would have been cost-effective, conclusions about cost-effectiveness are tenuous because Medicare costs were available only from 1991-93.

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INTRODUCTION

Prostate cancer is the most frequent cancer among American men and is the second leading cause of cancer-related deaths in all males.[1] With the advent of widespread screening with prostate-specific antigen (PSA), increasing numbers of men have been diagnosed with asymptomatic, localized, prostate cancer.[2] Among patients with clinically localized disease it is not known whether conservative management, i.e., "watchful waiting" or aggressive treatment, i.e., radiation therapy or radical prostatectomy, has better effectiveness. This is because men who are diagnosed with early stage prostate cancer may die of other causes before prostate cancer progresses enough to affect health. Both radical prostatectomy and radiation treatment have high rates of complications such as sexual impotence, urinary incontinence, and infection which adversely affect health. There is also a risk of surgical mortality with prostatectomy. Ideally, clinicians would identify men whose life expectancy was short enough that their prostate cancer would not be expected to progress substantially in their remaining lifetime. These men would receive conservative treatment (and no complications from aggressive treatment). For the rest, the benefit of aggressive treatment would be worth the risk of complications and they would receive aggressive treatment. However, although current prognostic factors for prostate carcinoma provide important information for patient care, the ideal method with which to incorporate the information attained from tumor-related factors (clinical stage, histologic grade, and PSA level), patient age, and comorbidity into a manageable prognostic score has not been found. The purpose of this study was to use instrumental variables techniques to estimate the outcome differences between aggressive treatment and conservative management among marginal patients with clinically localized disease; combine the health outcome and cost estimates to estimate true cost-effectiveness ratios; and using measured characteristics such as patient age, tumor grade, and the extent of co-morbid conditions, determine whether and what type of patients may be safely shifted from aggressive to conservative treatment.

BODY

The Statement of Work follows below. It was submitted and approved and a 1-year, no-cost extension was granted to complete tasks 4 and 5, which are now complete.

Task 1. Describe the factors that are related to the sorting of patients into conservative or aggressive treatments, Months 1-15.

a. Obtain data from SEER-HCFA linked databases and AMA Master File (Months 1-2).
b. Create analytic files (Months 3-4).
c. Construct and validate instrumental variables (Months 5-6).
d. Construct and validate treatment variables (Months 5-6).
e. Conduct analysis (Months 7-18) Examine patient-specific factors (demographic, co-morbidity, and tumor-related) and a series of factors related to treatment variation and theoretically unrelated to unmeasured confounders (candidate instrumental variables).
f. Prepare and submit manuscript (Months 19-21).

Task 2. Estimate unbiased treatment effects for marginal patients using instrumental variables techniques. Estimate for: (1) conservative vs. aggressive treatment and (2) given aggressive treatment, radiation vs. prostatectomy, Months 19-36,

a. Analyses of treatment effects on crude survival (Months 19-21).
b. Analyses of treatment effects on re-treatment-free survival (Months 20-36).
c. Analyses of treatment effects on Medicare costs (Months 23-36).
d. Prepare and submit manuscript (Months 26-36).

Task 3. Contrast the patient characteristics and treatment patterns across patients grouped by instrumental variables to describe the set of clinically localized prostate cancer patients who are at the practice margins for receiving aggressive treatment, Months 25-27.

a. Prepare tables for conservative vs. aggressive treatment (Month 25).
b. Prepare tables for radiation vs. prostatectomy, given aggressive treatment (Month 26).

Task 4. Combine the medical outcome and cost estimates to estimate true cost-effectiveness ratios to demonstrate whether aggressive treatments have been over- or under-utilized, Months 37-38.

a. Estimate cost-effectiveness ratios for conservative vs. aggressive treatment (Month 37-38).
b. Estimate cost-effectiveness ratios for radiation vs. prostatectomy, given aggressive treatment (Month 37-38).

Task 5. Policy paper and report writing, Months 38-42.

a. Prepare and submit a policy-oriented paper that presents cost-effectiveness and a detailed description of the marginal patients likely to be affected by shifts in treatment allocation algorithms (Month 38-41).
b. Prepare and submit the final project report (Month 42).

The personnel who have contributed to and been supported on this project are: Elizabeth A. Chrischilles, PhD (Principal Investigator), John Brooks, PhD (Co-principal investigator), Shane Scott, Pharm D (Investigator), Shari Chen-Hardee, MA (Statistician/Data Analyst), and Tae-Ryong Park (Data Analyst).

Task 1: Describe Factors Related to Choice of Aggressive vs. Conservative Treatment.

This task culminated in a manuscript titled "Age-specific effects of comorbidity, grade, and access on prostate cancer treatment choice." It is included in the Appendices to this report. It is currently in review by the National Cancer Institute (NCI) and the Centers for Medicare and Medicaid Services (CMS) for verification of confidentiality protection, as required in the project Data Use Agreement.

Briefly, men with advanced age, non-white race, higher comorbidity, low county mean income, and who lived relatively far from a prostatectomy hospital or radiation facility were less likely and men with higher tumor grade and high county HMO percent were more likely to receive aggressive treatment. The number of urologists per capita was significantly associated with aggressive treatment but the association was not linear. Aggressive treatment occurred in 74.8%, 68.1%, 40.3% and 7.6% of men aged 65-69, 70-74, 75-84, and 85+, respectively. Associations of treatment choice with tumor grade, comorbidity, and area/practice environment characteristics varied significantly among age groups; access to prostatectomy hospitals was most strongly associated with treatment choice among men under age 75 where treatment uncertainty is greatest. Under age 75, men who lived in rural areas were significantly more likely to receive aggressive treatment than those in non-rural areas. However, after age 84 rural men were less likely to receive aggressive treatment.

We concluded that incomplete evidence about which treatment (aggressive or conservative) provides optimal long-term outcomes for early stage prostate cancer is suspected to be an underlying reason for the associations of prostate cancer treatment choice with several non-clinical factors in this study. The influence of these factors and even their direction of association with aggressive treatment varied among age groups. Health policy should be tailored to these differences between age subgroups of older men.

Task 2: Unbiased Treatment Outcome Estimates for Marginal Patients Using Instrumental Variables Techniques

Overview of Instrumental Variable Estimation Techniques

In medical outcomes research, instrumental variable (IV) estimation[3,4] initially involves specifying a set of instrumental variables or "instruments" that satisfy the following two criteria:: (1) the variable must be related to the possibility of patients receiving a particular treatment; and (2) the variable must have no effect on outcomes either directly or indirectly (e.g., through relationships with unmeasured confounding factors such as patient severity and unrecorded treatments). The first criterion is necessary to observe treatment variation across patients grouped by the instrument and can be established by analysis of the available data. The second criterion is necessary to insure that treatment variation observed from grouping patients using the instrument is not related to confounding factors such as patient severity. Because many confounders are unmeasured, the second criterion must remain an assumption. Consequently, researchers must build a strong theoretical case for acceptance of the validity of the second criterion. Estimated correlations between instruments and measured confounders may be used to bolster the case.

If a single instrument is used that divides patients into two groups, treatment effects can be estimated through a simple comparison of treatment and outcome rates across the two groups. IV analysis is more powerful, though, if several instruments are used and comparisons are made simultaneously across many patient groups defined by the instruments. Two-stage least squares (2SLS) has been shown to be the optimal method to combine the effects of several instruments in a single analysis. Each treatment decision in this study was specified using the following two equation format and estimated using 2SLS:

Treatment Choice Equation: $T_i = \alpha + \gamma_1 * A_i + \gamma_2 * G_i + \gamma_3 * C_i + \gamma_4 * I_i + \varepsilon_i + \theta_i$

Outcome Equation: $O_i = \delta + \beta_1 * A_i + \beta_2 * G_i + \beta_3 * C_i + \beta_4 * T_i + v_i + \theta_i$

where:

O_i	=	1 if health outcome occurs (e.g. mortality within a time interval, re-treatment within a time interval), 0 otherwise. Cost equations will use total patient health care costs within the given time interval;
A_i	=	measured patient demographic characteristics;
G_i	=	measured tumor characteristics;
C_i	=	a set of binary variables based representing patient co-morbidities;
T_i	=	a binary variable equal to 1 if a patient received a specified treatment, 0 otherwise;
θ_i	=	unmeasured "confounding variables" that are related to both choice of treatment and outcomes;
ε_i, v_i	=	the net impact of unmeasured variables that distinctly affect treatment choices and health outcome, respectively;
I_i	=	a set of binary variables that group patients according to values of instrumental variables that affect outcomes only through their impact on treatment choice.

Our treatment variable T_i is a binary variable indicating whether the patient was treated. The objective is to obtain unbiased estimates of β_4. Because "θ" is in both the treatment and outcome equations, the estimate of the treatment choice parameter in equation (2) will be biased if ordinary least squares (OLS) is applied to equation 2.[5,6] In the first stage of the estimation procedure, the treatment choice equation (i.e., equation (1)) is estimated using ordinary least squares. Equation 1 includes a set of binary variables, I_i, that group patients based on the value of each patient's instruments. The predicted values of treatment probabilities from the first stage regressions for each patient, "T-hat" are then substituted for T_i in equation (2). In the second stage, equation (2) is estimated using OLS. Because A_i and G_i and C_i are specified in both equations, the only source of variation in T-hat used to estimate β_4 is the variation in treatment rates across patient groups defined by the instruments. In addition, because we assumed that the instruments are unrelated to the unmeasured confounding factors "θ", the estimate of β_4 that results from this process will be unbiased and attributable only to treatment rate differences across patients grouped by the set of instruments.

Evaluating the Validity of the Candidate Instrumental Variables

To be suitable instruments, variables must satisfy the following two criteria: (1) be related to the possibility of patients receiving a particular treatment and (2) have no effect on outcomes either directly or indirectly (e.g. through relationships with unmeasured confounding factors such as patient severity and unrecorded treatments). Because many confounders are unmeasured, the second criterion must remain an assumption. However, by comparing rates of *measured* confounders between groups of patients defined by the candidate instruments, we can provide evidence in support of the assumption. In the second annual report we displayed the results of these validation analyses (see "Evaluating the Validity of the Candidate Instrumental Variables" in the second annual report).

We demonstrated that patients who are aggressively treated are younger, have a higher tumor grade, earlier disease stage, and a lower prevalence of most co-morbidities than patients who are treated conservatively. In contrast, we demonstrated (Tables 2-8, Second Annual Report) that although patients who have greater access to aggressive treatments have a higher rate of aggressive treatment than patients with lower access, there is little systematic difference between these groups with respect to measured confounders, relative to the differences seen between the treated and untreated groups.

Results of the Instrumental Variables Analysis: Five-Year Survival.

Two sets of analyses are presented. The first set is the IV analysis of the effect on survival of aggressive treatment (radical prostatectomy or radiation treatment) vs. conservative treatment. The second set analyzes the effect of radiation vs. prostatectomy. Two-stage least squares IV analyses for five-year survival are presented. This extends the three-year survival results which were presented in the Second Annual Report. IV analysis of Medicare costs are covered in a later section (below). Analyses of re-treatment-free survival could not be conducted because the SEER-Medicare files were found to contain one year of data in which the diagnosis codes for physician bills were invalid.

The analysis of 5-yeaar survival included men patients who were age 66 and over at the time of diagnosis, who were presumed to have localized prostate cancer at the time of diagnosis and were HMO/Medicare appropriate over the whole study period, which was from the year prior to diagnosis till death or 5 years after diagnosis (n=32,939). By HMO/Medicare appropriate is meant that subjects were excluded from analysis if they had HMO or partial Medicare eligibility any time from the year before diagnosis to five years after diagnosis or death.

Two instrumental variables had satisfactory performance in models evaluating aggressive vs. conservative treatment: the number of prostatectomy hospitals per capita in a 40 mile radius of a man's residence (RP_RT40) and the number of urologists per capita in the county of residence (URO_RATE). The distributions of these variables are presented in Table 1 below. Three instrumental variables had satisfactory performance in models evaluating radical prostatectomy vs. radiation treatment: URO_RATE, distance to the nearest radiation treatment facility (RADDIST), and distance to the nearest hospital that performed prostatectomies (MRPDIST). The distributions of these three variables are presented in Table 2 below.

Table 1: Distributions of the two Instrumental Variables Used in Two-Stage Least Squares Analysis of Aggressive Vs. Conservative Treatment (n=32,939 men treated aggressively or conservatively).

Obs	VAR_NM	PCTL5	PCTL10	PCTL15	PCTL20	PCTL25	PCTL30	PCTL35	PCTL40	PCTL45	PCTL50
1	RP_RT40	0.000	0.0100	0.0102	0.0109	0.0132	0.0156	0.0165	0.0172	0.0185	0.0197
2	URO_RATE	0.000	0.0000	0.0367	0.0464	0.0613	0.0613	0.0613	0.0707	0.0764	0.0942

Obs	VAR_NM	PCTL55	PCTL60	PCTL65	PCTL70	PCTL75	PCTL80	PCTL85	PCTL90	PCTL95	PCTL100
1	RP_RT40	0.0207	0.0215	0.0229	0.0239	0.0261	0.0284	0.0305	0.0334	0.0386	3.000
2	URO_RATE	0.1016	0.1108	0.1180	0.1186	0.1213	0.1340	0.1638	0.1652	0.2644	102.818

Table 2: Distributions of the Three Instrumental Variables Used in Two-Stage Least Squares Analysis of Radical Prostatectomy Vs. Radiation Treatment, (n=17,497 men treated aggressively)

Obs	VAR_NM	PCTL5	PCTL10	PCTL15	PCTL20	PCTL25	PCTL30	PCTL35	PCTL40	PCTL45	PCTL50
1	URO_RATE	.0000	0.0000	0.0367	0.0573	0.0613	0.0613	0.0613	0.0745	0.0764	0.0942
2	RADDIST	.0000	0.0000	1.6514	2.4064	2.9322	3.3945	3.8218	4.3099	4.6908	5.2084
3	MRPDIST	.0000	0.0000	0.0000	0.0000	0.9432	1.8617	2.2642	2.6228	3.0316	3.3007

Obs	PCTL55	PCTL60	PCTL65	PCTL70	PCTL75	PCTL80	PCTL85	PCTL90	PCTL95	PCTL100
1	0.1016	0.1108	0.1180	0.1186	0.1213	0.1340	0.1638	0.1652	0.2308	102.818
2	5.7239	6.4078	7.4774	9.3620	11.9928	17.9942	28.1287	37.6587	61.2458	363.370
3	3.7263	4.2951	4.8297	5.7139	7.0510	9.0455	15.3406	24.9527	39.7558	280.567

Our findings from Task 1 and from preliminary examination of the 2SLS results confirmed that the IV had different relationships for different age groups. For this reason, all IV analyses were conducted separately for each age group (66-70, 71-75, 76-80, 81+). We examined the sensitivity of our results to the number of levels of each IV by repeating analyses for each IV from 20 levels (grouping every fifth percentile of the distribution) to two levels (grouping at the median). For each age group, the 2SLS analysis was repeated with all possible combinations of levels of the IV. All analyses controlled for age, race, tumor grade, county mean income, whether a rural county, and county HMO percent. The table below displays the results of one representative IV analysis per age group. All related analyses examining the different combinations of IV are included in the Appendices. The relevant Appendix number for each age group is indicated in the Table. Displayed in the table are the estimated treatment effect on five-year survival (TRT_EST) and its associated t test p-value (PROB_T), as well as the F statistic for overidentification and its associated p-value. A significant over-identification F test means that the IV have direct effects on outcome either through their own effects or through correlation with an unmeasured confounder. This is not desirable, since to be a valid IV, a variable should not be associated with treatment outcome.

Table 3. Representative Findings of Two-Stage Least Squares Analysis of Early Stage Prostate Cancer Treatment Effectiveness, By Age Group.

Obs	Age Group	N	IV definition	TRT_EST	PROB_T	F_OVERID	P_OVERID	Related Analyses
Aggressive Versus Conservative Treatment (n=32,939)								
1	66-70	9,726	RP_RT40 4 levels (quartiles); URO_RATE 10 levels (deciles)	0.275472	0.0044	1.45	0.1437	Appendix 2
2	71-75	10,473	RP_RT40 20 levels (5th percentiles); URO_RATE 5 levels (quintiles)	0.236383	0.0008	1.26	0.1823	Appendix 3
3	76-80	7,301	RP_RT40 4 levels (quartiles); URO_RATE 20 levels (5th percentiles)	0.180195	0.0175	1.12	0.3273	Appendix 4
4	81+	5,439	No significant treatment effect in any model					
Radical Prostatectomy Versus Radiation Treatment (n=17,497)								
5	66-70	6,845	RADDIST 4 levels (quartiles); URO_RATE and MRPDIST 10 levels (deciles)	-0.12557	0.0425	1.30	0.1719	Appendix 5
6	71-75	6,686	RADDIST 4 levels (quartiles); URO_RATE and MRPDIST 10 levels (deciles	-0.15141	0.0127	1.22	0.2267	Appendix 6
7	76-80	3,135	RADDIST 4 levels (quartiles); URO_RATE and MRPDIST 10 levels (deciles	-0.31253	0.0462	1.15	0.2917	Appendix 7
8	81+	831	Significant treatment effect in only one of 75 models					

The estimate TRT_EST in Table 3 above is for the coefficient, β_4, of "T-hat" (predicted treatment probability from the first stage). Because we assumed (and supported this assumption) that the instruments are unrelated to the unmeasured confounding factors, the estimate of β_4 is unbiased and attributable only to treatment rate differences across patients grouped by the set of instruments. This unbiased treatment effect can be interpreted as follows. For the treatment effect estimate of 0.275 seen among men age 66-70 (Table 3 row 1) this means that a 3.64 percentage point (1/0.275) increase in aggressive treatment rate will result in a one percentage point increase in five-year survival for men at the practice margins. For a treatment estimate of 0.18 (Table 3 row 3), this means that a 5.55 percentage point increase in aggressive treatment rate will result in a one percentage point increase in five-year survival among marginal patients of this age. As another way of looking at these results, since the estimates in Appendix 4 range from 0.15 to 0.20 (when the model is not over-identified and when the IV are related to treatment choice), for a population of 100 patients age 76-80, aggressive treatment of an additional 5 to 7 patients would result in one more patient surviving five years.

The treatment effect estimates for radiation vs. radical prostatectomy all have negative signs in Table 3. Because "treatment" in these analyses is radiation, which is being compared to radical prostatectomy, the negative sign means that five-year survival is significantly worse for radiation relative to surgery. This is particularly pronounced among those aged 76-80 (Table 3 row 7) where the treatment estimate is –0.31, meaning that a 3.2 percent DECREASE in radiation treatment (and substitution of radical prostatectomy) may be expected to result in a one percent increase in five-year survival among marginal patients aged 76-80 who are intended to receive aggressive treatment.

Task 3. Describing the Marginal Patients

We had a priori hypotheses about the subgroups of subjects who would have high treatment variation between high and low access areas. Theory predicts that treatment variation will be greatest for men with characteristics associated with the most uncertainty about the benefits of aggressive treatment.[7] Because older men with comorbidity and low tumor grade would have little expected benefit from treatment (overall life expectancy less than prostate cancer-specific life expectancy),[8] we expected that most providers would agree that these patients should not have aggressive treatments and there should be little treatment variation (low aggressive treatment rate regardless of access). Similarly, most providers will agree that young men with higher tumor grade and no co-morbidity may benefit from aggressive treatment and there should be little treatment variation (high aggressive treatment rate regardless of access).[8] Between these extremes there is uncertainty about the benefits of aggressive treatment and this should be reflected in greater treatment variation.

With the exception of race and income, interactions of age with each other variable in the models predicting treatment choice were statistically significant (p's < 0.05) (Appendix 1). The age-group-specific multivariable logistic regression models (Appendix 1) display this. In the two five-year age groups around age 70, the magnitude of the association between aggressive treatment and tumor grade, comorbidity, and access to prostatectomy hospitals was greater than for the older age groups. In contrast, access to radiation treatment was significantly associated with treatment choice only in the 75-84 year-old age group, and the magnitude of association with county HMO penetration was greatest for the oldest three age groups (age 70+). Though interacting statistically with age (p=0.023), in all four age groups, men residing in the third urologists per capita quartile of counties were significantly less likely to receive aggressive treatment. Men under age 75 were more likely to receive aggressive treatment if they lived in a rural county; those age 85 and over were less likely to be treated aggressively if they lived in a rural county.

Guided by these hypotheses and by the supporting finding of different relationships with treatment choice among age subgroups, all IV analyses were age-group-specific. The absence of a treatment effect in the oldest age group (age 81+) and the presence of a treatment effect among younger men (age 66-80) indicates that uncertainty is greatest for those aged 66-80 and that policy initiatives to increase aggressive treatments (or, among those treated aggressively, initiatives to increase radical prostatectomies) would be expected to improve survival for this age group. Hence, these analyses suggest that aggressive treatments are under-utilized among men age 66-80 and that, among the group of men this age who are intended for aggressive treatment, radiation therapy is over-utilized relative to radical prostatectomy.

Men under age 66 were not studied. It might be expected that at some younger age treatment choice is clear and that clinicians may be sorting patients optimally to receive aggressive treatments. However, in the age range observed in this dataset, optimal sorting appeared to occur only among the oldest old. For the rest, radical prostatectomy appears to be under-utilized.

Task 4. Cost-Effectiveness Analyses.

Using instrumental variable estimation methods, earlier tasks estimated the effect of aggressive treatment relative to conservative treatment for marginal presumed localized early stage prostate cancer patients. In addition, we also estimated the effect of surgery relative to radiation treatment for marginal patients that were aggressively treated. Our results suggest that an increase in aggressive treatment for patients with presumed localized early stage prostate cancer would have resulted in increased survival rates but these effects decreased with patient age. We also showed that an increase in surgery among those patients aggressively treated would have also increased survival and these effects increased with patient age.

Because aggressive treatment of presumed localized early stage prostate cancer patients and surgery for aggressively-treated presumed localized early stage prostate cancer patients may involve additional treatment costs, it is not clear whether the survival benefits from treatment we have observed justify initiating policies to increase treatment rates. Cost effectiveness analysis (CEA) is needed to help policy-makers decide whether the costs of achieving additional survival benefits are justified. Table 4 demonstrates the scenarios when a CEA analysis is required. CEA is required when either (1) a treatment provides improved health outcome and costs more, or (2) a treatment provides a lower health outcome but costs less.

Table 4. Conditions to Perform a Cost-effectiveness Analysis (CEA) Related to Outcomes and Cost.

	Treatment Health Outcome Vs. Alternative	
Treatment Cost Vs. Alternative	Better	Worse
Higher	Do CEA	Reject Treatment
Lower	Accept Treatment	Do CEA

CEA requires estimates of the differences in costs that can be attributable to each treatment arm. Because of the known strong association between treatment choice and patient comorbidities in presumed localized early stage prostate cancer patients (e.g. those not receiving aggressive treatments generally have much greater illness severity) estimating cost differences by directly comparing average 5-year costs between treat and untreated groups may bias this estimate significantly. For example, the comparison of 5-year costs between aggressively-treated and conservatively-managed patients will probably understate the costs attributable to aggressive treatment as the aggressively-treated patients will have less comorbidity-related costs.

This research requires estimates of the cost differences that reflect the set of patients whose treatment choices are affected by the instrumental variables used in our analysis. As such, our goal is to obtain instrumental variable estimates of the effect of treatment choice on 5-year costs. Empirically, this means substituting 5-year cost estimates for each patient in the outcome equation (specified in Task 2) and estimating the model again using 2SLS.

We approached estimating the 5-year cost estimates for each patient from the policy-maker's or Medicare administrator's perspective. As such, our goal was to include all Medicare reimbursements for each patient in the 5-year period after and including the patient's diagnosis month. This includes reimbursements (Medicare payment amount) from all inpatient institutional, outpatient institutional, physician, and home health claims attributable to each patient during this period. Unfortunately, after collecting the available SEER-Medicare claims we found that the universe of physician claims in the SEER-Medicare databases were not available prior to 1991. This limited our IV cost analysis to only those patients that were diagnosed from 1991 to 1993. Table 5 provides the mean 5-year total cost by age group and whether patients had aggressive or conservative treatment. Table 6 provides the mean 5-year cost totals for aggressively-treated patients by age group and whether the patients had surgery or radiation treatment.

Table 5: Average Medicare Reimbursements for Presumed Localized Prostate Cancer Patients, 1991-1993, by Age and Treatment

	Conservative (patients)	Aggressive (patients)	Patients
66-70	35,843.87 (1,019)	35,134.97 (4,221)	5,240
71-75	37,672.83 (1,446)	37,405.98 (4,153)	5,599
76-80	37,929.20 (1,789)	37,787.63 (1,854)	3,643
81+	36,305.76 (1,845)	39,216.10 (470)	2,315

Table 6: Average Medicare Reimbursements for Aggressively-Treated Presumed Localized Prostate Cancer Patients, 1991-1993, by Age and Treatment			
	Surgery (patients)	Radiation (patients)	Patients[a]
66-70	33,210.14 (2,581)	37,888.06 (1,453)	4,034
71-75	35,224.57 (1,623)	38,756.70 (2,429)	4,052
76-80	36,106.13 (268)	38,033.39 (1,574)	1,842
81+	40,376.50 (37)	39,120.82 (432)	469
a. Patients receiving both surgery and radiation in their first course of therapy were excluded.			

Because our IV cost models were estimated using only a subset of the data used in our survival models, we believe that few inferences can be made from contrasting the our survival and cost estimates in a CEA. In addition, the smaller sample sizes in our cost analysis provided less information to accurately identify cost differences between groups, and we found weaker relationships between treatment choice and our instruments. We also found that many of the cost models estimated using the smaller sample size have over-identification statistics sufficiently large enough to indicate that the identifying assumptions of the model (the instruments are not directly related to cost) have been violated. As a result, the inferences that can be made from these estimates should be discounted accordingly. With these qualifications stated, we thought it would be instructive to apply the CEA rules in Table 4 and contrast these estimates with the survival estimates found in Table 3. Table 7 contains IV cost estimates using the IV specifications that coincide with the survival models in Table 3 As with Table 3, the table entries were representative of a much larger set of analyses such as those in Appendices 2-7.

Table 7: Two-Stage Least Squares Estimates of Presumed Localized Prostate Cancer Cost Estimates, by Age Group.								
Model	Age Group	Obs	Estimate	Prob_T	Overidentification F	P Overid	Instrument F	P Instruments
Aggressive Treatment Cost Effect vs Conservative Treatment								
1	66-70	5,240	-94,690.30	<.0001	1.61	0.0885	2.777	0.0009
2	71-75	5,599	29,258.53	0.0178	1.63	0.0324	2.197	0.0008
3	76-80	3,643	6,396.03	0.3325	2.31	0.0013	5.628	0.0001
4	81+	No significant treatment effects. Cost model not run.						
Radiation Treatment Cost Effect vs. Radical Prostatectomy								
5	66-70	4,034	30,386.36	0.0004	3.06	0.0001	3.763	0.0001
6	71-75	4,052	28,071.25	0.0001	2.07	0.0041	5.612	0.0001
7	76-80	1,842	35,934.70	0.0009	1.78	0.0204	4.304	0.0001
8	81+	No significant treatment effects. Cost model not run.						

For the 66-70 year old age group, a consistently negative 5-year cost estimate was found for aggressive treatment relative to conservative treatment for marginal patients. The negative coefficient on costs suggests that increased aggressive treatment would have been a 5-year cost saver for this age group. However, the over-identification problem suggests that perhaps part of this decrease may stem from less costly patients being treated aggressively. If these estimation problems did not exist, a negative cost result coupled with a positive and significant survival benefit from increased aggressive treatment, suggests that the aggressive treatment rate should have been increased for this age group during this time period.

The 71-75 and the 76-80 age groups both have positive 5-year cost estimates for aggressive relative to conservative treatment. The over-identification problem remains. Both age groups also had significant survival benefits from increased aggressive treatment (Table 3). In these scenarios, a CEA is required to provide information for policy-makers to decide whether increased aggressive rates are worth the added costs. The numbers translate into $123,775.94 (29,258.53/.236) per additional 71-75 year-old patient attaining 5-year survival, and $35,495.03 (6,396.03/.180) per additional 76-80 year-old patient attaining 5-year survival.

For all three age groups of aggressively treated patients, radiation treatment had lower survival benefits (Table 3) and greater treatment costs relative to surgery for marginal patients. Following our CEA rules, radiation treatments should have been decreased relative to surgery for aggressively treated patients.

Once again, it should be made clear that the because of differences in the samples across the survival and cost models, and the rejection of our identifying restrictions in the cost models with the smaller sample sizes, our CEA estimates should be given little weight. They were provided merely for instructive purposes. Future research with larger samples that are consistent between models will be necessary to provide sufficient estimates to aid policy-makers. The SEER-Medicare database linkage will soon be updated for diagnoses through 1999. This would provide the opportunity to expand the sample size available for these analyses, in addition to providing more recent treatment patterns.

Task 5. Final Report and Policy Analysis Paper

Acceptance of this final report completes task 5. Based on the findings from Tasks 1-4, we combined the policy implications and the IV analysis into one manuscript.

KEY RESEARCH ACCOMPLISHMENTS

Key research accomplishments included:

- Acquiring, downloading, reading, and documenting the numerous files from the SEER-Medicare linked data for all prostate cancers from eleven SEER registries;
- Obtaining the zip code and years of operation for all radiation treatment centers in the eleven SEER areas;
- Locating and obtaining a detailed data dictionary that was not provided with the data. Researching the voluminous data dictionary to understand the Medicare files;
- Constructing and validating a case selection algorithm to apply the study inclusion and exclusion criteria;
- Evaluating data quality of key variables;
- Constructing candidate instrumental variables from the Medicare data, Area Resource File, and Radiation Treatment Center zip code locations;
- Demonstrating that selected attributes of patients' residence area (the candidate instrumental variables) group patients such that the groups have different rates of aggressive treatment but do not differ meaningully in demographic, tumor, or comorbidity characteristics supporting the conclusion that the IV analyses yield unbiased estimates of treatment effect for patients at the practice margins;

- Demonstrating that when patients are grouped according to these IV, higher survival rates are observed for those IV groupings that have a higher prevalence of aggressive treatment;

- Determined that increased survival can be expected if aggressive treatment and in particular radical prostatectomy is increased for patients at the practice margins;

- Documented that the estimated treatment benefits apply to categories of men who a priori theory predicted to be at the practice margins because of a higher degree of uncertainty about treatment benefit: men aged 66-80.

- Discovered that aspects of the environment that surrounds the patient-physcian relationship are significantly associated with receipt of aggressive treatment for early stage prostate cancer. However these associations vary in magnitude and even in direction among age subgroups after age 65. To be effective, health policy interventions may need to be tailored to the age subgroup.

- Synthesized economic and survival data to estimate cost-effectiveness of aggressive treatments, finding that a larger sample size will be required to answer cost-effectiveness questions validly due to absence of pre-1991 physician claims data.

REPORTABLE OUTCOMES

The SEER-Medicare linked database is very large and complex. We have developed experience working with the data and have developed a library of programs and files. This will increase the efficiency of analyses for future projects. A series of technical reports have been produced and are periodically shared with other researchers interested in these data. Two abstracts have been accepted for presentation at the American Urological Association Annual Meeting in Orlando, Florida, May 25-30 (Appendix 8). In addition to this work, we have recently received funding to apply these methods to the study of the effectiveness of adjuvant chemotherapy for non-small cell lung cancer.

Previous researchers have documented that factors other than prognostic patient characteristics (age, grade, and comorbidity) influence treatment choices. A unique contribution of our work has been the theoretically predicted and empirically demonstrated finding that these factors vary with patient age, implying that health policy interventions may need to be tailored to the age subgroup. A further unique contribution of our work is that it not only documents that area characteristics representing access to providers of aggressive treatments predict treatment choice, but also it documents that these practice variations are associated with different five-year survival rates and demonstrates that the unbiased IV treatment effect estimates pertain to men aged 66 to 80 who constitute 80 percent of Medicare beneficiaries with prostate cancer. Only for men over age 80 does it appear that aggressive treatments in general and radical prostatectomy in particular are not under-utilized. For the remainder, five-year survival may be expected to increase one percent for a 4 to 7 percent increase in aggressive treatments among marginal patients.

CONCLUSION

Aggressive treatment appears to be underutilized for early stage prostate cancer. For geographic areas with low aggressive treatment rates, clinicians should consider increasing aggressive treatment among men aged 65 to 80. Among men intended for aggressive treatments, clinicians in areas with low radical prostatectomy rates relative to radiation treatment rates should consider increasing radical prostatectomy relative to radiation therapy. If, after all relevant clinical factors (e.g. PSA level) are considered, the clinician who practices in an area with low aggressive treatment rate is still undecided about whether to recommend aggressive treatment for a man with these characteristics, these data suggest that aggressive treatment with radical prostatectomy should be selected.

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APPENDICES

Appendix 1. Manuscript in Review.

AGE-SPECIFIC EFFECTS OF COMORBIDITY, GRADE, AND ACCESS ON PROSTATE CANCER TREATMENT CHOICE

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ABSTRACT

Background. Prostate cancer-specific survival and overall survival are closest among men aged 65 to 74. Uncertainty about whether to treat conservatively (i.e. watchful waiting) or aggressively (radiation or radical prostatectomy) was theorized to be greatest at this age and aspects of the healthcare environment that surrounds a patient/physician relationship were theorized to influence treatment choice differently among age groups.

Objectives. To examine factors associated with practice variation in the choice between aggressive and conservative management of clinically localized prostate cancer and whether age modifies these associations.

Methods. Data were from the SEER-Medicare linked database. Men (n=30,886) were diagnosed with clinically localized prostate cancer during 1986-1993. Age, race, aggressive treatment (radiation; radical prostatectomy) and tumor grade (Well, Moderately, and Poorly differentiated) were from SEER. Charlson comorbidity score was based on Medicare hospital claims diagnoses. Access to radical prostatectomy and radiation facilities was the distance from a man's residence to the relevant healthcare provider. County-level variables from the 1990 Area Resource File were mean income, percent HMO enrollment, urologists per capita and percent rural residences.

Results. Men with advanced age, non-white race, higher comorbidity, low county mean income, and who lived relatively far from a prostatectomy hospital or radiation facility were less likely and men with higher tumor grade and high county HMO percent were more likely to receive aggressive treatment. The number of urologists per capita was significantly associated with aggressive treatment but the association was not linear. Aggressive treatment occurred in 74.8%, 68.1%, 40.3% and 7.6% of men aged 65-69, 70-

74, 75-84, and 85+, respectively. Associations of treatment choice with tumor grade, comorbidity, and area/practice environment characteristics varied significantly among age groups; access to prostatectomy hospitals was most strongly associated with treatment choice among men under age 75 where treatment uncertainty is greatest. Under age 75, men who lived in rural areas were significantly more likely to receive aggressive treatment than those in non-rural areas. However, after age 84 rural men were less likely to receive aggressive treatment.

Conclusion. Incomplete evidence about which treatment (aggressive or conservative) provides optimal long-term outcomes for early stage prostate cancer is suspected to be an underlying reason for the associations of prostate cancer treatment choice with several non-clinical factors in this study. The influence of these factors and even their direction of association with aggressive treatment varied among age groups. Health policy should be tailored to these differences between age subgroups of older men.

INTRODUCTION

Prostate cancer is the most frequent cancer among American men and is the second leading cause of cancer-related deaths in all males.[1] With the advent of widespread screening with prostate-specific antigen (PSA), increasing numbers of men have been diagnosed with asymptomatic, localized, prostate cancer.[2] Accompanying this increase has been a striking change in treatment patterns. The adjusted rate of radical prostatectomy in 1990 was 5.75-fold greater than in 1984.[3]

Among patients with localized disease it is not known whether "aggressive treatment," i.e., radiation therapy or radical prostatectomy, affords significantly better outcomes than conservative treatment, i.e., "watchful waiting". For many older men, the risk of developing hormone-resistant metastatic disease is low and many suggest that the risks of aggressive treatment may not be justified due to lack of a significant gain in longevity.[4-6] Men with low-grade, smaller tumors are likely to have organ-confined disease. Some of these men can possibly benefit from aggressive treatment provided that age and co-morbidity suggest a significant longevity.[7] Others have suggested survival advantages with aggressive treatment of poorly differentiated tumors. Although tumor-related prognostic factors provide important information for patient care,[8] the ideal method to incorporate the information attained from tumor-related factors (clinical stage, histologic grade, and PSA level), age, and comorbidity into a manageable prognostic score has not been found.

The paucity of evidence and resulting uncertainty about how to treat early stage prostate cancer has likely contributed to the substantial treatment variation that has been documented..[3,9-11] It is now well-documented for many health conditions that treatment variation is not random but rather that places are associated with a treatment "signature."[12,13]

There are several reasons why the environment that surrounds a patient-physician relationship may affect the treatment decisions that result from that relationship. Such concepts include: (1) uncertainty which allows for greater treatment discretion among the providers to which a patient has access,[14-16] (2) predominant health insurance market characteristics that may affect how all patients in an area are treated,[17,18] (3) the number of communication channels available to the provider,[19] and (4) area socioeconomic structure influencing resources available to patients.[20]

Desch et al.[21] showed using Virginia Cancer Registry data that aggressive treatment was negatively related to patient age and their number of comorbidities and was positively related to the average income of the zip code containing the patient residence and year of diagnosis. Provider counts (radiation oncologists and urologists) in the county of patient residence did not affect treatment choices. Distance to the nearest radiation oncologist did not affect the choice of aggressive treatment but lowered the probability that hormonal therapy (orchiectomy) was used instead of aggressive treatment. Klabunde et al.[22] demonstrated relationships between aggressive treatment and the patient's race and the average educational attainment in the area surrounding the patient's residence and found lower rates of aggressive treatment in the cancer registry areas that included states with high rural populations. Potosky et al[23] used data from Seattle and San Francisco and showed that HMO Medicare patients were more likely to receive aggressive treatment than Medicare fee-for-service patients. None of these studies took into consideration the potential modifying effects of age on these relationships.

At age 70 prostate cancer-specific survival and overall survival are closest[7] and uncertainty may be theorized to be greatest due to the vagaries of accurately determining the net effect of age and comorbidity on life expectancy. We therefore hypothesized that tumor grade, comorbidity, and aspects of the healthcare system or practice environment would have the greatest effect on treatment choice near this age.

The purpose of this study was to examine factors associated with practice variation in the choice between aggressive and conservative management of clinically localized prostate cancer and whether age modifies this association. This research focuses on aspects of the healthcare system or practice environment that surrounds a patient/physician relationship.

METHODS

Data Sources

Data for this study were obtained from the Surveillance, Epidemiology, and End Results (SEER) program and from Medicare claims that have been linked with SEER data for approximately 93 percent of persons with cancer aged 65 and older at the time of cancer diagnosis.[24] The linkage includes all cases reported by the registries through 1996 and Medicare claims through 1998. SEER is funded by the National Cancer Institute. Participating registries collect data for all cancer patients diagnosed within their defined geographic area. Data include month and year of diagnosis, age at diagnosis, race, tumor stage and grade, and initial (first four months post-diagnosis) cancer treatments. The Patient Entitlement and Diagnosis Summary File (PEDSF) is the file in the SEER-Medicare linked database that includes all of the SEER-derived data. Medicare files from the Centers for Medicare and Medicaid Services (CMS) included demographic and enrollment information and all bills submitted for inpatient hospital care, outpatient hospital care, and physician services. The diagnoses on inpatient bills (coded using the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM)) were the source of co-morbidity information for this report. County-level area characteristic variables were constructed from the 1990 Bureau of Health Professions' Area Resource File (http://www.arfsys.com/).

Sample Selection

Prostate cancer cases were included from population-based SEER cancer registries in four states (Connecticut, Iowa, New Mexico, and Utah) and four metropolitan areas (Atlanta, Georgia; Detroit, Michigan; San Francisco-Oakland, California; and San Jose, California). Men with prostate cancer were identified who met the following inclusion criteria: diagnosed between 1986 and 1993, age 65 or older at the time of diagnosis, first primary prostate cancer, zip code of residence in the geographic area of the included registries, and either received radical prostatectomy or the tumor stage was coded as local. Men who received radical prostatectomy were included even if the tumor stage was not coded as local. They were considered to have been initially presumed to have localized disease.[25] This assumption was required because SEER records only the most definitive stage, hence cases who may have been initially presumed to have clinically localized disease may have been "up-staged" following surgery due to a higher pathologic stage. There were 44,222 men who met these inclusion criteria (38,885 had a tumor stage coded as local and 5,337 had tumor stage other than local but were treated with radical prostatectomy). Men were excluded (n=11,120) if they did not have full Medicare coverage throughout the time period (n= 6,043) or if they had HMO enrollment (n=5,712). A further 2,216 cases were excluded due to grade IV (n=262) or unknown tumor grade (n=1,954). Men with grade IV (undifferentiated) tumors were excluded due to the small sample size and because they could not be appropriately combined for analysis with men having grade III (poorly differentiated) tumors. There were 30,886 cases remaining after application of these criteria.

Variable Definition

Cases were considered to have had aggressive treatment (n=17,068) if they had either radiation treatment or radical prostatectomy designated in the PEDSF file. Conservative treatment (n=13,818) included those for whom it was known that neither radical prostatectomy nor radiation treatment were received (cases whose radiation or surgery treatment status were unknown had been excluded from eligibility).

Demographic variables included age at diagnosis and race. Age and race were obtained from the PEDSF file and were individual-level variables. Clinical characteristics included the tumor grade and co-morbidity. Tumor grade was as recorded by SEER as well-differentiated (corresponding to Gleason score 2-4), moderately differentiated (Gleason score 5-7), or poorly differentiated (Gleason score 8-10). Comorbid conditions were any condition except prostate cancer present on inpatient bills during the one year before diagnosis and excluding the date of diagnosis. Co-morbidity was represented as a modified Charlson score[26] where a higher score indicates a greater burden of co-morbid illness.

Concepts regarding the environment that surround a patient-physician relationship included (1) the types of providers to which a patient has access, (2) the predominant health insurance market characteristics in the area, (3) the number of communication channels available to the provider, and (4) area socioeconomic structure. We studied the following indicators of these concepts, respectively: (1) distance a patient would have to travel to reach the nearest radiation treatment facility during the diagnosis year as well as a patient's differential distance to the nearest prostatectomy hospital (distance to the nearest hospital that performed prostatectomies minus distance to the nearest non-prostatectomy hospital), (2) percent HMO enrollment in the county, (3) number of urologists per capita in the county, and (4) county mean income.

The county mean income and percent of residents enrolled in HMOs was from the ARF as was the number of urologists per capita (number of urologists in 1990 in the county of the patient's residence divided by the average number of prostate cancer patients diagnosed per year during 1985-1993 in the county). Also from the ARF, a county was classified as rural if any percent of its residences were rural residences and non-rural otherwise.

Distances were calculated as the straight-line distance from the longitude and latitude for the centroid of the subject's residence zip code to the longitude and latitude of for the centroid of the zip code of the relevant hospital or radiation treatment facility. The number of radical prostatectomies performed by each hospital in the geographic region was determined from the Medicare files. From this each hospital was classified as a radical prostatectomy hospital if it provided any radical prostatectomy in the calendar year.

Statistical Analysis

Distance measures, county mean income and urologists per capita were grouped by quartile and the first quartile was used as the reference category in all analyses. The percent of population enrolled in an HMO was three groups with cutoffs at the 50^{th} and 75^{th} percentile because of its skewed distribution (25^{th} percentile was 0%). Charlson score was dichotomized as score>0 vs. score= 0. Race was grouped as White (reference), Black, Native American, Asian, and Other except in age-group-specific models where it was categorized as White and Non-White due to small sample sizes. Single variable logistic regression tested the univariate associations of each independent variable with whether aggressive or conservative treatment was received. Multivariable logistic regression analysis of the odds of aggressive vs. conservative treatment was used to estimate the effect of the patient-physician environment measures after controlling for patient age, race, and clinical characteristics. Interactions of age with other independent variables and subsequent age-group-specific multivariable logistic regression models tested the specified hypotheses about the modifying effects of age.

RESULTS

Table 1 displays characteristics of study subjects by whether aggressive treatment was received. Younger patients, those with higher grade tumors, less comorbidity, and white race, were more likely to be aggressively treated. In addition, patients who lived in non-rural areas, areas with higher mean income, higher HMO penetration, and greater access to prostatectomy hospitals, radiation treatment facilities and urologists were more likely to receive aggressive treatment.

Multivariable logistic regression (Table 2) found aggressive treatment decreased markedly with advancing age and presence of comorbidity. Aggressive treatment was much more likely for higher grade tumors. Native American, Black, and Asian men were significantly less likely to receive aggressive treatment than white men, controlling for other variables. The healthcare system/practice environment factors all remained significantly associated with treatment choice but county rurality was no longer significantly associated with treatment choice. Men residing in the highest HMO penetration quartile of counties were significantly more likely to undergo aggressive treatment. Men residing in the highest three income quartiles of counties were significantly more likely to undergo aggressive treatment than were men in the lowest income quartile. Those whose relative access (differential distance) to prostatectomy hospitals was least (i.e. the distance to a prostatectomy hospital was more than 3.2 miles farther than the distance to a non-prostatectomy hospital) were significantly less likely to receive aggressive treatments than were those who lived relatively closer to a prostatectomy hospital. Those with the farthest distance to travel to reach a radiation treatment facility were significantly less likely to receive aggressive treatments. Finally, urologists per capita exhibited a significant relationship with aggressive treatment where areas with more urologists per capita were less likely to receive aggressive treatment.

With the exception of race and income, interactions of age with each other variable in the model were statistically significant (p's < 0.05). The age-group-specific multivariable logistic regression models (Table 3) display this. In the two five-year age groups around age 70, the magnitude of the association between aggressive treatment and tumor grade, comorbidity, and access to prostatectomy hospitals was greater than for the older age groups. In contrast, access to radiation treatment was significantly associated with treatment choice only in the 75-84 year-old age group, and the magnitude of association with county HMO penetration was greatest for the oldest three age groups (age 70+). Though interacting statistically with age (p=0.023), in all four age groups, men residing in the third urologists per capita quartile of counties were significantly less likely to receive aggressive treatment. Men under age 75 were more likely to receive aggressive treatment if they lived in a rural county; those age 85 and over were less likely to be treated aggressively if they lived in a rural county.

DISCUSSION

The decision of whether to treat early stage prostate cancer aggressively (i.e. with radiation or prostatectomy) or conservatively (watchful waiting) among older men is made based on life expectancy and consideration of possible adverse sequelae of treatment. Median remaining survival time at age 70 is 12 years and at 75 is 9.4 years (http://www.cdc.gov/nchs/products/pubs/pubd/lftbls/decenn/1991-89.htm), which is also approximately equal to prostate-cancer survival at that age.[7] The rate of tumor growth is such that in men older than 75 or with significant comorbidity, prostate cancer-specific life expectancy exceeds overall life expectancy.[7] For this reason, and because of the high incidence of adverse sequelae of aggressive treatments,[27,28] most clinicians suggest that avoidance of aggressive treatments among men over 75 or with significant comorbidity may be a reasonable option. Tumor grade, associated with more rapidly growing tumors, has the effect of lowering the age for this equilibrium and suggesting treatment benefits from treatment at somewhat older ages.

Clinical uncertainty is associated with practice variation.[12-16] When the evidence base supporting a treatment decision is not strong, non-clinical factors may become predictors of whether a treatment is used. Incomplete evidence about which treatment (aggressive or conservative) provides optimal long-term outcomes for early stage prostate cancer is suspected to be an underlying reason for the associations of prostate cancer treatment choice with several non-clinical factors in this study. Higher county mean income and HMO penetration were both associated with a greater probability that a man would have aggressive treatment (radiation or prostatectomy) as were living closer to a prostatectomy hospital than to a non-prostatectomy hospital and living closer to a radiation treatment facility.

Klabunde et al[22] previously demonstrated that low census tract SES was associated with lower rates of aggressive treatment (but not with the form of treatment, i.e., radiation vs. prostatectomy). Area mean income may serve in our analyses as a proxy for measurement at the individual level. An alternative view is that differences in the socioeconomic position of counties reflect more than individual compositional effects but rather are closely related to the physical and social attributes of the community to which individuals have access. Studies that measure socioeconomic position simultaneously at the individual and community level have recently attested to this extraindividual effect of area socioeconomic factors,[29-33] finding, for example, that residence in a poverty area confers a 50% increase in nine year mortality, even after controlling for a large number of individual characteristics.[33]

Age-group-specific multivariate analysis found that, among men under age 75, rural residence was associated with increased probability of aggressive treatment whereas among those age 85+ rural residence was associated with a decreased probability of aggressive treatment. These analyses controlled not only for tumor grade and comorbidity but also area income, healthcare market structure, and several measures of access to providers. Previous reports on treatment of other cancers have found that rural areas have lower treatment rates, possibly related to distance to treatment facilities.[34] Our findings indicate that additional reasons for rural-urban differences in treatment rates should be explored beyond distance to treatment facilities, clinical characteristics, and socioeconomic characteristics. Patient preferences are a category of characteristics that may be fruitful for further investigation to inform rural health policy. For example, previous research on rural residents suggests that they seem to be more self-reliant or prefer to self-treat illnesses.[35-38.]

Multivariate analyses that collapsed across age gave a misleading impression that rural residence was not associated with aggressive treatment rate after controlling for clinical and socioeconomic characteristics and access to providers. It may be that the interaction between age and rural residence explains the apparent inconsistencies in the literature regarding rural/urban status and aggressive treatment rates for early stage prostate cancer. Klabunde et al[22] reported the aggressive treatment rate for more rural SEER areas such as Iowa, Connecticut, Hawaii, and New Mexico to be much lower than in more urban areas such as Atlanta, Detroit, and Seattle after adjusting for clinical and socioeconomic characteristics. In contrast, Desch et al[21] found in Virginia that residing in an urban county was associated with a lower probability of aggressive treatment after adjusting for clinical and socioeconomic characteristics and for access to providers. Harlan et al[34] observed rural-urban differences in aggressive treatment rates in the Prostate Cancer Outcomes Study.

The finding that higher HMO penetration in the patient's county of residence was associated with aggressive treatment may reflect the practices, guidelines, and policies of HMOs per se, or may be a marker for generally greater access to healthcare in these areas. However, analyses of county HMO percent was adjusted (in Tables 2 and 3) for access to radiation treatment and prostatectomy hospitals and for urologists per capita, and therefore does not appear to be a proxy for access to aggressive treatments. Potosky et al[23] found HMO patients more likely than fee-for-service (FFS) patients to receive aggressive therapy in one geographic area but not in another. In both areas, HMO patients were much more likely to receive radiation than prostatectomy among those given aggressive treatment. These authors suggested that, due to the incomplete evidence base for selecting treatment, factors that may explain HMO-FFS differences in treatment include: availability of resources under HMO vs. FFS, practice style differences, communication among physicians, and incentive differences between HMO and FFS systems. We excluded men with Medicare HMO coverage from our study. Therefore the effect of HMO penetration must be interpreted as "spillover" of HMO practice patterns to affect the care of non-HMO residents of an area. Our findings extend those of Potosky et al[23] to include a greater diversity of HMO structures and to demonstrate that the predominance of an HMO healthcare insurance arrangement in an area affects how all patients in an area are treated. Because of time constraints, providers may adopt "usual" practice patterns or rules-of-thumb reflecting the predominant healthcare insurance arrangement in an area.[17,18,39] It is noteworthy that the association of HMO penetration with treatment choice was greatest among the oldest men where treatment choice is presumably least uncertain. The findings of Potosky et al[23] suggest that this may be due to a greater tendency by HMO providers to use radiation treatments which many clinicians feel to be associated with fewer side effects than prostatectomy for the oldest patients.[27,28]

The number of urologists in a man's county divided by the average annual number of prostate cancer patients residing in the county (urologists per capita) was associated with treatment choice, but not in a continuously increasing fashion. This indicator was selected as a measure of available communication channels between urologists and, hence, hypothesized to be associated with a greater adoption/diffusion of an innovative, preferred treatment.[19] During the years of this study, the innovation in treatment was to question whether prostatectomy is warranted among older men. Hence, an inverse association might be expected between urologists per capita and use of aggressive treatment among Medicare-aged men. Further, this association might be expected to be strongest for the oldest of these. However, we found an inverse association only for the third quartile of county urologists per capita and no association for the second and fourth quartiles. A potential explanation for this finding is that in addition to providing more communication channels for providers, more urologists per capital also leads to more competition across providers. Competition can be expected to *increase* the rate of active treatments in general. The direction of this effect would oppose the direction of the communication channels and could explain the non-monotonic direction of association.

The distance a patient lived from a hospital that performed prostatectomies relative to their distance from a hospital that did not was selected as a measure of the preferences of the providers to which a patient has access. Living relatively father from hospitals that tended to prefer prostatectomies was associated with a decreased probability of aggressive treatment. This effect was accentuated among men under age 75 where uncertainty about the long-term outcomes of aggressive treatment is presumably greatest. Similarly, living farther from a radiation treatment facility was associated with a lower probability of aggressive treatment. The effect of access to radiation treatment facilities was accentuated among men aged 75-84, perhaps because many clinicians feel radiation is safer than prostatectomy for the oldest patients.[27,28]

While life expectancy at particular ages can be accurately estimated from US Life Tables, this is only of limited assistance to clinicians. First, life expectancy is an estimate of the median remaining years of life at a particular age; 50% of men can be expected to survive longer. Second, the effect of any particular comorbidity or comorbidities on remaining life years is not tabulated for clinicians. As expected, we found presence of comorbidity and tumor grade to have the strongest association with treatment choice during the ages in which prostate-cancer-specific survival is closest to overall survival. But are clinicians optimally using this clinical information (age, comorbidity and tumor grade) along with PSA level to determine which patients will benefit from aggressive treatment? Given the lack of quantitative information about the effect of particular comorbidities, we suspect that this sorting of patients is not optimal. The finding that access to prostatectomy hospitals was most strongly related to treatment choice at this age (under 75), supports that uncertainty about aggressive treatment with radical prostatectomy was greatest for these men where the association with comorbidity and tumor stage is greatest.

CONCLUSION

Aspects of the environment that surrounds the patient-physcian relationship are significantly associated with receipt of aggressive treatment for early stage prostate cancer. However these associations vary in magnitude and even in direction among age subgroups after age 65. To be effective, health policy interventions may need to be tailored to the age subgroup. From age 65-84, uncertainty about effectiveness of radical prostatectomy (age 65-74) and the relative effectiveness of radical prostatectomy vs. radiation treatment (age 75-84) should be addressed. Are aggressive treatments over-utilized? Among men who are aggressively treated, is radical prostatectomy over- or under-utilized relative to radiation treatment? Future research using instrumental variables analysis is one way to address these questions for the most policy-relevant group of men: those who would be treated were they to reside in a "high access" environment but not treated in a "low access" environment. Health policy should also be informed by attention to the possible co-variation of patient preferences with geographical location, which may suggest different policy for rural vs. non-rural areas.

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Table 1. Description of Study Subjects

		n	Conservative % (n=13,818)	Aggressive % (n=17,068)
Age	95+	55	98.2	1.8
	90-94	380	95.3	4.7
	85-89	1,603	91.6	8.4
	80-84	3,956	76.7	23.3
	75-79	7,598	50.8	49.2
	70-74	10,087	31.9	68.1
	65-69	7,207	25.2	74.8
Race	White	27,471	43.8	56.2
	Black	2,813	54.5	45.5
	Native American	45	73.3	26.7
	Asian	171	50.3	49.7
	Other	386	32.4	67.6
Grade	III: Poorly differentiated	5,496	39.2	60.8
	II: Moderately differentiated	15,966	35.1	64.9
	I: Well differentiated	9,424	63.7	35.7
Comorbidity	Charlson score>0	3,873	62.0	38.0
	Charlson score=0	27,013	42.3	57.7
County HMO enrollment, %	>21.223	8,586	38.5	61.5
	17.290 to 21.223	6,833	45.5	54.5
	<17.290	15,467	47.9	52.1
County mean yearly income, $	>23,937	7,706	39.6	60.4
	18,787 to 23,937	7,205	44.1	55.9

	15,949 to 18,787	8,200	4.03	56.7
	<15,949	7,775	52.0	48.0
Differential distance to prostatectomy hospital, miles	Farthest (>3.215)	7,774	50.7	49.3
	0 to 3.215	5,998	44.5	55.5
	-2.162 to 0	9,415	42.9	57.2
	Closest (<-2.162)	7,699	41.2	58.8
Distance to radiation treatment facility, miles	>12.7	7,717	49.7	50.3
	5.3-12.7	7,607	42.4	57.6
	2.9-5.2	7,925	42.4	57.6
	<2.9	7,637	44.4	55.6
County urologists per prostate cancer patient	>0.147	7,827	40.3	59.7
	0.107 to 0.147	7,538	46.7	53.3
	0.065 to 0.107	8,966	44.6	55.4
	< 0.065	6,555	48.0	52.0
Whether rural county	Rural county	15,015	46.2	53.9
	Non-rural county	15,871	43.4	56.6

Table 2. Multivariate Logistic Regression Results of Factors Associated with Receiving Aggressive Treatment for Early Stage Prostate Cancer.

		Adjusted Odds Ratio	95% Confidence Interval
Age	95+	0.005	0.001,0.037
	90-94	0.014	0.008,0.022
	85-89	0.03	0.023,0.032
	80-84	0.09	0.08,0.10
	75-79	0.30	0.28,0.33
	70-74	0.71	0.66,0.76
	65-69	1.00	-
Race	Other	1.13	0.88,1.44
	Asian	0.66	0.47,0.94
	Native American	0.34	0.16,0.72
	Black	0.46	0.42,0.51
	White	1.00	-
Grade	III: Poorly differentiated	3.76	3.47,4.07
	II: Moderately differentiated	3.74	3.52,3.97
	I: Well differentiated	1.00	-
Comorbidity	Charlson score>0	0.51	0.47,0.55
	Charlson score=0	1.00	-
County HMO enrollment, %	>21.223	1.26	1.18,1.36
	17.290 to 21.223	1.01	0.93,1.09
	<17.290	1.00	-
County mean yearly income, $	>23,937	1.41	1.28,1.55

	18,787 to 23,937	1.14	1.05,1.24
	15,949 to 18,787	1.25	1.16,1.35
	<15,949	1.00	-
Differential distance to prostatectomy hospital, miles	>3.215	0.83	0.77,0.91
	0 to 3.215	0.96	0.88,1.04
	-2.162 to 0	0.99	0.92,1.07
	<-2.162	1.00	-
Distance to radiation treatment facility, miles	>12.7	0.85	0.77,0.95
	5.3-12.7	1.05	0.97,1.14
	2.9-5.2	1.02	0.95,1.11
	<2.9	1.0	-
County urologists per prostate cancer patient	>0.147	0.91	0.82,1.01
	0.107 to 0.147	0.66	0.60,0.73
	0.065 to 0.107	1.03	0.97,1.1.15
	< 0.065	1.0	-
Whether rural county	Rural county	1.03	0.96,1.11
	Non-rural county	1.0	-

Table 3. Adjusted Odds Ratios (95% Confidence Intervals) By Age Group

	65-69 (n=7,207)	70-74 (n=10,087)	75-84 (n=11,554)	85+ (n=2,038)
% Aggressive	74.8	68.1	40.3	7.6
Non-white race (vs. white)	1.11 (0.70,1.75)	0.74 (0.54,1.00)	1.13 (0.86, 1.48)	1.94 (0.71,5.31)
Grade:				
Poorly differentiated grade	6.07 (5.03,7.33)	4.22 (3.68,4.85)	2.28 (2.03,2.55)	2.37 (1.43,3.93)
Moderately differentiated grade	5.26 (4365,5.96)	4.31 (3.91,4.76)	2.46 (2.24,2.70)	2.46 (1.56,3.88)
Well-differentiated grade	1.0	1.0	1.0	1.0
Co-morbidity:				
Charlson score > 0	0.43 (0.36,0.51)	0.47 (0.41,0.54)	0.55 (0.49,0.61)	0.84 (0.52,1.35)
Charlson score = 0	1.0	1.0	1.0	1.0
County HMO enrollment, %:				
>21.223	1.11 (0.95,1.29)	1.36 (1.20, 1.54)	1.36 (1.22,1.52)	1.66 (1.04,2.64)
17.290 to 21.223	0.90 (0.75,1.07)	0.97 (0.85,1.11)	1.13 (1.01,1.27)	1.37 (0.83,2.25)
<17.290	1.0	1.0	1.0	1.0
County mean yearly income, $:				
>23,937	1.04 (0.85,1.28)	1.62 (1.38,1.91)	1.42 (1.24,1.63)	1.30 (0.71,2.37)
18,787 to 23,937	1.12 (0.93,1.35)	1.13 (0.98,1.30)	1.10 (0.97,1.25)	0.94 (0.55,1.61)
15,949 to 18,787	1.04 (0.87,1.23)	1.31 (1.15,1.50)	1.27 (1.13,1.43)	0.70 (0.41,1.18)
<15,949	1.0	1.0	1.0	1.0
Differential distance[a] to prostatectomy:				
Farthest quartile (>3.2 miles)	0.70 (0.58,0.84)	0.68 (0.59,0.78)	0.88 (0.78,1.00)	0.90 (0.51,1.60)
3rd quartile (0 to 3.2 miles)	0.76 (0.64,0.91)	0.79 (0.69,0.91)	1.01 (0.89,1.14)	0.93 (0.53,1.63)

2nd quartile (-2.2 to 0 miles)	0.95 (0.81,1.12)	0.89 (0.79,1.01)	0.99 (0.88,1.10)	1.40 (0.88,2.24)
1st quartile (<-2.2 miles)	1.0	1.0	1.0	1.0
Distance to radiation treatment facility, miles				
>12.7	1.12 (0.90,1.41)	0.86 (0.72,1.03)	0.80 (0.69,0.93)	1.64 (0.66,2.72)
5.3-12.7	1.25 (1.05,1.48)	0.95 (0.83,1.09)	0.97 (0.87,1.09)	1.75 (1.07,2.87)
2.9-5.2	1.15 (0.97,1.35)	1.02 (0.90,1.17)	1.03 (0.92,1.15)	1.25 (0.76,2.05)
<2.9	1.0	1.0	1.0	1.0
County urologists per prostate cancer patient:				
>0.147	0.82 (0.66,1.03)	0.80 (0.68,0.95)	0.99 (0.86,1.15)	0.60 (0.31,1.17)
0.107 to 0.147	0.71 (0.57,0.89)	0.64 (0.54,0.75)	0.68 (0.59,0.79)	0.43 (0.22,0.84)
0.065 to 0.107	0.80 (0.66,1.97)	0.91 (0.78,1.05)	1.03 (0.91,1.17)	0.91 (0.53,1.58)
< 0.065	1.0	1.0	1.0	1.0
Whether rural county				
Rural county	1.12 (0.96,1.30)	1.29 (1.14,1.46)	1.07 (0.97,1.19)	0.61 (0.39, 0.97)
Non-rural county	1.0	1.0	1.0	1.0

[a] Differential distance was calculated as the distance to the nearest hospital that performed prostatectomies minus the distance to the nearest hospital that did not perform prostatectomies.

Appendix 2. Detailed Instrumental Variables Analyses Tables For All Possible Combinations of Levels of Instrumental Variables, Men Aged 66-70, Analyses of the Effect of Aggressive Vs. Conservative Treatment.

Table 1 Results of Two-Stage Least Squares Analysis, Men Aged 66-70, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped at the 5th Percentile (20 groups). For example, in row 2, the results are for the model including RP_RT40 in 10 groups (grouped in deciles) and URO_RATE in 20 groups (grouped every 5th percentile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.303063	<.0001	1.21	0.1832	2.5963	0.0002	4.67571	.0001
2	RP_RT40	10%	0.316821	<.0001	1.33	0.1290	3.6210	0.0002	5.87319	.0001
3	RP_RT40	20%	0.287095	0.0005	1.61	0.0441	3.6975	0.0052	6.44400	.0001
4	RP_RT40	25%	0.297475	0.0003	1.57	0.0593	6.5258	0.0002	7.03871	.0001
5	RP_RT40	50%	0.266598	0.0011	1.43	0.1193	16.2608	0.0001	7.67078	.0001
6	URO_RATE	5%	0.303063	<.0001	1.21	0.1832	6.8473	0.0001	4.67571	.0001
7	URO_RATE	10%	0.288679	0.0007	1.10	0.3238	7.5410	0.0001	4.34895	.0001
8	URO_RATE	20%	0.381404	0.0015	0.99	0.4737	2.4391	0.0448	2.75492	.0001
9	URO_RATE	25%	0.310488	0.0094	1.08	0.3618	2.6657	0.0461	2.80000	.0001
10	URO_RATE	50%	0.367034	0.0037	1.02	0.4343	3.2616	0.0710	2.84246	.0001

Table 2 Results of Two-Stage Least Squares Analysis, Men Aged 66-70 with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in deciles (10 groups). For example, in row 3, the results are for the model including RP_RT40 in 5 groups (grouped in quintiles) and URO_RATE in 10 groups (grouped every decile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.288679	0.0007	1.10	0.3238	2.3656	0.0007	4.34895	.0001
2	RP_RT40	10%	0.300912	0.0009	1.14	0.3040	3.3446	0.0004	5.93822	.0001
3	RP_RT40	20%	0.257963	0.0082	1.47	0.1268	3.5267	0.0070	6.98508	.0001
4	***RP_RT40***	***25%***	***0.275472***	***0.0044***	***1.45***	***0.1437***	***5.4447***	***0.0010***	***7.75492***	***.0001***
5	RP_RT40	50%	0.234316	0.0165	1.22	0.2761	13.0454	0.0003	8.97602	.0001
6	URO_RATE	5%	0.316821	<.0001	1.33	0.1290	6.5813	0.0001	5.87319	.0001
7	URO_RATE	10%	0.300912	0.0009	1.14	0.3040	7.2777	0.0001	5.93822	.0001
8	URO_RATE	20%	0.458874	0.0009	0.88	0.5697	2.3798	0.0494	3.89935	.0001
9	URO_RATE	25%	0.351818	0.0090	1.06	0.3885	2.8189	0.0375	4.13574	.0001
10	URO_RATE	50%	0.437037	0.0029	0.89	0.5332	2.9397	0.0865	4.40969	.0001

Table 3 Results of Two-Stage Least Squares Analysis, Men Aged 66-70, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in quintiles (5 groups). For example, in row 4, the results are for the model including RP_RT40 in 4 groups (grouped in quartiles) and URO_RATE in 5 groups (grouped every quintile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.381404	0.0015	0.99	0.4737	2.2399	0.0015	2.75492	.0001
2	RP_RT40	10%	0.458874	0.0009	0.88	0.5697	3.3213	0.0005	3.89935	.0001
3	RP_RT40	20%	0.432867	0.0073	1.45	0.1801	3.9198	0.0035	4.55749	.0001
4	RP_RT40	25%	0.479242	0.0027	1.17	0.3217	5.9527	0.0005	5.52077	.0001
5	RP_RT40	50%	0.388048	0.0180	1.16	0.3260	13.4403	0.0002	6.84448	.0001
6	URO_RATE	5%	0.287095	0.0005	1.61	0.0441	6.4715	0.0001	6.44400	.0001
7	URO_RATE	10%	0.257963	0.0082	1.47	0.1268	7.2834	0.0001	6.98508	.0001
8	URO_RATE	20%	0.432867	0.0073	1.45	0.1801	2.8330	0.0231	4.55749	.0001
9	URO_RATE	25%	0.270469	0.0866	1.76	0.1036	3.1829	0.0229	4.95356	.0001
10	URO_RATE	50%	0.381564	0.0330	1.91	0.1065	3.4933	0.0616	5.72176	.0001

Table 4 Results of Two-Stage Least Squares Analysis, Men Aged 66-70, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in quartiles (4 groups). For example, in row 5, the results are for the model including RP_RT40 in 2 groups (split at the median) and URO_RATE in 4 groups (grouped every quartile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.310488	0.0094	1.08	0.3618	2.4001	0.0006	2.80000	.0001
2	RP_RT40	10%	0.351818	0.0090	1.06	0.3885	3.7371	0.0001	4.13574	.0001
3	RP_RT40	20%	0.270469	0.0866	1.76	0.1036	4.6741	0.0009	4.95356	.0001
4	RP_RT40	25%	0.320254	0.0434	1.66	0.1400	6.3948	0.0003	5.86092	.0001
5	RP_RT40	50%	0.197686	0.2295	1.28	0.2808	15.1761	0.0001	7.78847	.0001
6	URO_RATE	5%	0.297475	0.0003	1.57	0.0593	6.7964	0.0001	7.03871	.0001
7	URO_RATE	10%	0.275472	0.0044	1.45	0.1437	7.5725	0.0001	7.75492	.0001
8	URO_RATE	20%	0.479242	0.0027	1.17	0.3217	3.4662	0.0078	5.52077	.0001
9	URO_RATE	25%	0.320254	0.0434	1.66	0.1400	3.4638	0.0156	5.86092	.0001
10	URO_RATE	50%	0.462572	0.0121	1.44	0.2293	3.7725	0.0521	7.13374	.0001

Table 5. Results of Two-Stage Least Squares Analysis, Men Aged 66-70, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in quartiles (4 groups). For example, in row 1, the results are for the model including RP_RT40 in 20 groups (grouped every 5^{th} percentile) and URO_RATE in 2 groups (grouped at the median).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.367034	0.0037	1.02	0.4343	2.4120	0.0005	2.8425	.0001
2	RP_RT40	10%	0.437037	0.0029	0.89	0.5332	3.6755	0.0001	4.4097	.0001
3	RP_RT40	20%	0.381564	0.0330	1.91	0.1065	4.4008	0.0015	5.7218	.0001
4	RP_RT40	25%	0.462572	0.0121	1.44	0.2293	5.8427	0.0006	7.1337	.0001
5	RP_RT40	50%	0.333208	0.0763	0.55	0.4577	14.1842	0.0002	12.5948	.0001
6	URO_RATE	5%	0.266598	0.0011	1.43	0.1193	6.8828	0.0001	7.6708	.0001
7	URO_RATE	10%	0.234316	0.0165	1.22	0.2761	7.7279	0.0001	8.9760	.0001
8	URO_RATE	20%	0.388048	0.0180	1.16	0.3260	3.5294	0.0070	6.8445	.0001
9	URO_RATE	25%	0.197686	0.2295	1.28	0.2808	3.6845	0.0115	7.7885	.0001
10	URO_RATE	50%	0.333208	0.0763	0.55	0.4577	5.0974	0.0240	12.5948	.0001

Appendix 3. Detailed Instrumental Variables Analyses Tables For All Possible Combinations of Levels of Instrumental Variables, Men Aged 71-75, Analyses of the Effect of Aggressive Vs. Conservative Treatment.

Table 1 Results of Two-Stage Least Squares Analysis, Men Aged 71-75, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped at the 5th Percentile (20 groups). For example, in row 2, the results are for the model including RP_RT40 in 10 groups (grouped in deciles) and URO_RATE in 20 groups (grouped every 5th percentile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.230737	0.0001	1.39	0.0669	4.4127	.0001	7.4185	.0001
2	RP_RT40	10%	0.222658	0.0005	1.46	0.0672	5.5625	.0001	9.0188	.0001
3	RP_RT40	20%	0.228209	0.0008	1.63	0.0412	6.2335	.0001	10.0002	.0001
4	RP_RT40	25%	0.239694	0.0006	1.94	0.0096	4.9868	.0019	9.9937	.0001
5	RP_RT40	50%	0.217123	0.0022	1.49	0.0932	9.5830	.0020	10.8497	.0001
6	URO_RATE	5%	0.230737	0.0001	1.39	0.0669	9.9939	.0001	7.4185	.0001
7	URO_RATE	10%	0.233854	0.0002	1.56	0.0329	14.9511	.0001	8.3618	.0001
8	URO_RATE	20%	0.236383	0.0008	1.26	0.1823	22.3662	.0001	8.2025	.0001
9	URO_RATE	25%	0.3095	0.0002	1.28	0.1785	13.1058	.0001	6.2748	.0001
10	URO_RATE	50%	0.313096	0.0003	1.26	0.1990	28.4501	.0001	6.3547	.0001

Table 2 Results of Two-Stage Least Squares Analysis, Men Aged 71-75 with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in deciles (10 groups). For example, in row 3, the results are for the model including RP_RT40 in 5 groups (grouped in quintiles) and URO_RATE in 10 groups (grouped every decile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.233854	0.0002	1.56	0.0329	4.5417	0.0001	8.3618	.0001
2	RP_RT40	10%	0.232958	0.0007	1.75	0.0279	5.6336	0.0001	11.0100	.0001
3	RP_RT40	20%	0.234367	0.0014	2.10	0.0142	6.4155	0.0001	13.2968	.0001
4	RP_RT40	25%	0.251331	0.0011	2.63	0.0023	3.5755	0.0133	13.1438	.0001
5	RP_RT40	50%	0.223481	0.0039	1.90	0.0480	6.7897	0.0092	15.3762	.0001
6	URO_RATE	5%	0.222658	0.0005	1.46	0.0672	10.5530	0.0001	9.0188	.0001
7	URO_RATE	10%	0.232958	0.0007	1.75	0.0279	15.7408	0.0001	11.0100	.0001
8	URO_RATE	20%	0.237946	0.0024	1.61	0.0809	23.6895	0.0001	11.6190	.0001
9	URO_RATE	25%	0.328012	0.0008	1.65	0.0790	14.3397	0.0001	8.2531	.0001
10	URO_RATE	50%	0.349171	0.0010	1.76	0.0697	29.5189	0.0001	8.5475	.0001

Table 3 Results of Two-Stage Least Squares Analysis, Men Aged 71-75, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in quintiles (5 groups). For example, in row 4, the results are for the model including RP_RT40 in 4 groups (grouped in quartiles) and URO_RATE in 5 groups (grouped every quintile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.236383	0.0008	1.26	0.1823	4.4325	0.0001	8.2025	.0001
2	RP_RT40	10%	0.237946	0.0024	1.61	0.0809	5.2088	0.0001	11.6190	.0001
3	RP_RT40	20%	0.233752	0.0058	2.14	0.0364	6.2341	0.0001	16.1170	.0001
4	RP_RT40	25%	0.249595	0.0054	3.08	0.0051	3.7325	0.0107	16.4387	.0001
5	RP_RT40	50%	0.210174	0.0206	1.63	0.1644	7.6584	0.0057	22.3033	.0001
6	URO_RATE	5%	0.228209	0.0008	1.63	0.0412	10.4461	0.0001	10.0002	.0001
7	URO_RATE	10%	0.234367	0.0014	2.10	0.0142	15.5615	0.0001	13.2968	.0001
8	URO_RATE	20%	0.233752	0.0058	2.14	0.0364	24.0631	0.0001	16.1170	.0001
9	URO_RATE	25%	0.325607	0.0031	2.36	0.0279	15.1924	0.0001	11.1581	.0001
10	URO_RATE	50%	0.356948	0.0041	3.09	0.0149	29.8628	0.0001	12.4699	.0001

Table 4 Results of Two-Stage Least Squares Analysis, Men Aged 71-75, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in quartiles (4 groups). For example, in row 5, the results are for the model including RP_RT40 in 2 groups (split at the median) and URO_RATE in 4 groups (grouped every quartile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.3095	0.0002	1.28	0.1785	4.2985	.0001	6.2748	.0001
2	RP_RT40	10%	0.328012	0.0008	1.65	0.0790	4.7574	.0001	8.2531	.0001
3	RP_RT40	20%	0.325607	0.0031	2.36	0.0279	5.4929	.0002	11.1581	.0001
4	RP_RT40	25%	0.352513	0.0024	3.47	0.0039	5.0666	.0017	11.8840	.0001
5	RP_RT40	50%	0.277637	0.0223	1.88	0.1314	6.9969	.0082	15.7669	.0001
6	URO_RATE	5%	0.239694	0.0006	1.94	0.0096	10.1944	.0001	9.9937	.0001
7	URO_RATE	10%	0.251331	0.0011	2.63	0.0023	14.5579	.0001	13.1438	.0001
8	URO_RATE	20%	0.249595	0.0054	3.08	0.0051	22.1151	.0001	16.4387	.0001
9	URO_RATE	25%	0.352513	0.0024	3.47	0.0039	14.9339	.0001	11.8840	.0001
10	URO_RATE	50%	0.404705	0.0028	4.92	0.0021	27.2976	.0001	13.4402	.0001

Table 5. Results of Two-Stage Least Squares Analysis, Men Aged 71-75, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in quartiles (4 groups). For example, in row 1, the results are for the model including RP_RT40 in 20 groups (grouped every 5th percentile) and URO_RATE in 2 groups (grouped at the median).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.313096	0.0003	1.26	0.1990	4.3992	0.0001	6.3547	.0001
2	RP_RT40	10%	0.349171	0.0010	1.76	0.0697	4.6772	0.0001	8.5475	.0001
3	RP_RT40	20%	0.356948	0.0041	3.09	0.0149	4.7610	0.0008	12.4699	.0001
4	RP_RT40	25%	0.404705	0.0028	4.92	0.0021	3.4955	0.0149	13.4402	.0001
5	RP_RT40	50%	0.347932	0.0144	4.27	0.0389	4.0798	0.0434	23.6679	.0001
6	URO_RATE	5%	0.217123	0.0022	1.49	0.0932	10.6726	0.0001	10.8497	.0001
7	URO_RATE	10%	0.223481	0.0039	1.90	0.0480	15.5676	0.0001	15.3762	.0001
8	URO_RATE	20%	0.210174	0.0206	1.63	0.1644	24.4776	0.0001	22.3033	.0001
9	URO_RATE	25%	0.277637	0.0223	1.88	0.1314	16.5077	0.0001	15.7669	.0001
10	URO_RATE	50%	0.347932	0.0144	4.27	0.0389	33.8088	0.0001	23.6679	.0001

Appendix 4. Detailed Instrumental Variables Analyses Tables For All Possible Combinations of Levels of Instrumental Variables, Men Aged 76-80, Analyses of the Effect of Aggressive Vs. Conservative Treatment.

Table 1 Results of Two-Stage Least Squares Analysis, Men Aged 76-80, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped at the 5th Percentile (20 groups). For example, in row 2, the results are for the model including RP_RT40 in 10 groups (grouped in deciles) and URO_RATE in 20 groups (grouped every 5th percentile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.194309	0.0063	1.30	0.1139	1.9461	0.0081	5.79471	.0001
2	RP_RT40	10%	0.189773	0.0121	1.69	0.0185	1.4743	0.1511	7.15174	.0001
3	RP_RT40	20%	0.163307	0.0331	1.08	0.3639	1.9821	0.0944	8.67229	.0001
4	RP_RT40	25%	0.180195	0.0175	1.12	0.3273	3.9635	0.0078	9.34322	.0001
5	RP_RT40	50%	0.159794	0.0411	1.18	0.2790	0.9450	0.3310	9.78656	.0001
6	URO_RATE	5%	0.194309	0.0063	1.30	0.1139	9.8935	0.0001	5.79471	.0001
7	URO_RATE	10%	0.202732	0.0101	1.55	0.0337	13.3387	0.0001	5.87064	.0001
8	URO_RATE	20%	0.162004	0.1035	1.54	0.0509	14.4654	0.0001	4.42812	.0001
9	URO_RATE	25%	0.164531	0.1556	1.74	0.0197	10.3410	0.0001	3.40238	.0001
10	URO_RATE	50%	0.295163	0.0275	1.54	0.0616	13.7477	0.0002	2.87426	.0001

Table 2 Results of Two-Stage Least Squares Analysis, Men Aged 76-80 with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in deciles (10 groups). For example, in row 3, the results are for the model including RP_RT40 in 5 groups (grouped in quintiles) and URO_RATE in 10 groups (grouped every decile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.202732	0.0101	1.55	0.0337	1.8614	0.0128	5.8706	.0001
2	RP_RT40	10%	0.197583	0.0207	2.25	0.0023	1.2019	0.2887	7.7539	.0001
3	RP_RT40	20%	0.155781	0.0749	1.51	0.1112	0.9491	0.4343	10.1934	.0001
4	RP_RT40	25%	0.176389	0.0403	1.62	0.0862	2.8528	0.0359	11.4482	.0001
5	RP_RT40	50%	0.151018	0.0887	1.82	0.0599	0.0505	0.8223	12.8755	.0001
6	URO_RATE	5%	0.189773	0.0121	1.69	0.0185	9.4838	0.0001	7.1517	.0001
7	URO_RATE	10%	0.197583	0.0207	2.25	0.0023	12.5151	0.0001	7.7539	.0001
8	URO_RATE	20%	0.132794	0.2306	2.51	0.0027	13.8024	0.0001	6.3040	.0001
9	URO_RATE	25%	0.132342	0.3136	2.97	0.0006	10.4895	0.0001	4.8440	.0001
10	URO_RATE	50%	0.332776	0.0418	2.74	0.0034	12.4438	0.0004	3.9041	.0001

Table 3 Results of Two-Stage Least Squares Analysis, Men Aged 76-80, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in quintiles (5 groups). For example, in row 4, the results are for the model including RP_RT40 in 4 groups (grouped in quartiles) and URO_RATE in 5 groups (grouped every quintile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.162004	0.1035	1.54	0.0509	1.7374	0.0242	4.4281	.0001
2	RP_RT40	10%	0.132794	0.2306	2.51	0.0027	1.4677	0.1536	6.3040	.0001
3	RP_RT40	20%	0.052192	0.6537	1.06	0.3892	1.4835	0.2043	9.3319	.0001
4	RP_RT40	25%	0.091204	0.4225	1.24	0.2814	3.0385	0.0279	11.1252	.0001
5	RP_RT40	50%	0.032618	0.7880	1.32	0.2585	0.2039	0.6516	13.7799	.0001
6	URO_RATE	5%	0.163307	0.0331	1.08	0.3639	10.0412	0.0001	8.6723	.0001
7	URO_RATE	10%	0.155781	0.0749	1.51	0.1112	13.3095	0.0001	10.1934	.0001
8	URO_RATE	20%	0.052192	0.6537	1.06	0.3892	15.5044	0.0001	9.3319	.0001
9	URO_RATE	25%	0.022866	0.8759	1.64	0.1311	11.5448	0.0001	6.7467	.0001
10	URO_RATE	50%	0.283024	0.1474	0.71	0.5836	14.2802	0.0002	5.3681	.0001

Table 4 Results of Two-Stage Least Squares Analysis, Men Aged 76-80, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in quartiles (4 groups). For example, in row 5, the results are for the model including RP_RT40 in 2 groups (split at the median) and URO_RATE in 4 groups (grouped every quartile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.164531	0.1556	1.74	0.0197	1.9510	0.0079	3.4024	.0001
2	RP_RT40	10%	0.132342	0.3136	2.97	0.0006	2.2644	0.0158	4.8440	.0001
3	RP_RT40	20%	0.022866	0.8759	1.64	0.1311	2.3771	0.0497	6.7467	.0001
4	RP_RT40	25%	0.096529	0.4897	2.04	0.0693	4.5411	0.0035	8.5614	.0001
5	RP_RT40	50%	-0.04505	0.7844	2.30	0.0748	0.3050	0.5808	9.4978	.0001
6	URO_RATE	5%	0.180195	0.0175	1.12	0.3273	9.9262	0.0001	9.3432	.0001
7	URO_RATE	10%	0.176389	0.0403	1.62	0.0862	13.1955	0.0001	11.4482	.0001
8	URO_RATE	20%	0.091204	0.4225	1.24	0.2814	14.8487	0.0001	11.1252	.0001
9	URO_RATE	25%	0.096529	0.4897	2.04	0.0693	10.9836	0.0001	8.5614	.0001
10	URO_RATE	50%	0.314967	0.0784	0.77	0.5080	13.9854	0.0002	8.0900	.0001

Table 5. Results of Two-Stage Least Squares Analysis, Men Aged 76-80, with Two Instrumental Variables (RP_RT40 and URO_RATE) Controlling for Covariates, Where the Instrumental Variable Not Named in the Row is Grouped in quartiles (4 groups). For example, in row 1, the results are for the model including RP_RT40 in 20 groups (grouped every 5th percentile) and URO_RATE in 2 groups (grouped at the median).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	RP_RT40	5%	0.295163	0.0275	1.54	0.0616	1.8829	0.0114	2.8743	.0001
2	RP_RT40	10%	0.332776	0.0418	2.74	0.0034	1.9284	0.0436	3.9041	.0001
3	RP_RT40	20%	0.283024	0.1474	0.71	0.5836	1.2941	0.2698	5.3681	.0001
4	RP_RT40	25%	0.314967	0.0784	0.77	0.5080	3.5588	0.0137	8.0900	.0001
5	RP_RT40	50%	0.244787	0.2577	1.75	0.1858	0.0025	0.9603	10.8301	.0001
6	URO_RATE	5%	0.159794	0.0411	1.18	0.2790	10.3098	0.0001	9.7866	.0001
7	URO_RATE	10%	0.151018	0.0887	1.82	0.0599	14.1495	0.0001	12.8755	.0001
8	URO_RATE	20%	0.032618	0.7880	1.32	0.2585	16.8752	0.0001	13.7799	.0001
9	URO_RATE	25%	-0.04505	0.7844	2.30	0.0748	12.1994	0.0001	9.4978	.0001
10	URO_RATE	50%	0.244787	0.2577	1.75	0.1858	20.2698	0.0001	10.8301	.0001

Appendix 5. Detailed Instrumental Variables Analyses Tables For All Possible Combinations of Levels of Instrumental Variables, Men Aged 66-70, Analyses of the Effect of Radical Prostatectomy Vs. Radiation Treatment.

Table 1 Results of Two-Stage Least Squares Analysis, Men Aged 66-70, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped at the 5th Percentile (20 groups). For example, in row 2, the results are for the model including URO_RATE in 10 groups (grouped in deciles), RADDIST in 20 groups (grouped every 5th percentile) and MRPDIST in 20 groups (grouped every 5th percentile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.13802	0.0037	1.35	0.0519	9.3899	0.0001	5.12724	.0001
2	URO_RATE	10%	-0.11319	0.0460	1.37	0.0582	8.1544	0.0001	4.14976	.0001
3	URO_RATE	20%	-0.03281	0.6344	1.37	0.0682	4.2724	0.0019	3.19347	.0001
4	URO_RATE	25%	-0.02798	0.6952	1.39	0.0601	3.0476	0.0275	3.06212	.0001
5	URO_RATE	50%	-0.03202	0.6597	1.41	0.0563	5.0112	0.0252	3.11812	.0001
6	RADDIST	5%	-0.13802	0.0037	1.35	0.0519	1.6806	0.0354	5.12724	.0001
7	RADDIST	10%	-0.13367	0.0056	1.32	0.0855	2.6094	0.0052	6.08954	.0001
8	RADDIST	20%	-0.13826	0.0049	1.42	0.0516	3.5775	0.0064	6.67660	.0001
9	RADDIST	25%	-0.13675	0.0056	1.51	0.0294	4.1448	0.0061	6.81294	.0001
10	RADDIST	50%	-0.14219	0.0045	1.58	0.0197	5.8957	0.0152	7.02312	.0001
11	MRPDIST	5%	-0.13802	0.0037	1.35	0.0519	3.1973	0.0001	5.12724	.0001
12	MRPDIST	10%	-0.1404	0.0036	1.13	0.2615	5.4988	0.0001	5.93385	.0001
13	MRPDIST	20%	-0.1372	0.0051	1.20	0.1914	9.1194	0.0001	6.35797	.0001
14	MRPDIST	25%	-0.1401	0.0049	1.18	0.2103	9.6028	0.0001	6.31710	.0001
15	MRPDIST	50%	-0.13636	0.0073	1.15	0.2498	19.7336	0.0001	6.41271	.0001

Table 2 Results of Two-Stage Least Squares Analysis, Men Aged 66-70, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped in Deciles (10 groups). For example, in row 3, the results are for the model including URO_RATE in 5 groups (grouped in quintiles), RADDIST in 10 groups (grouped in deciles) and MRPDIST in 10 groups (grouped in deciles).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.13333	0.0064	1.03	0.4134	10.0514	0.0001	7.37094	.0001
2	URO_RATE	10%	-0.11067	0.0614	1.05	0.3942	9.1772	0.0001	6.31412	.0001
3	URO_RATE	20%	-0.02548	0.7366	1.05	0.3982	4.9836	0.0005	4.80104	.0001
4	URO_RATE	25%	-0.01344	0.8657	1.06	0.3875	3.6840	0.0115	4.59229	.0001
5	URO_RATE	50%	-0.0277	0.7348	1.05	0.3933	5.6112	0.0179	4.79800	.0001
6	RADDIST	5%	-0.12373	0.0335	1.14	0.2640	2.2941	0.0014	4.84381	.0001
7	RADDIST	10%	-0.11067	0.0614	1.05	0.3942	3.9845	0.0001	6.31412	.0001
8	RADDIST	20%	-0.12369	0.0438	1.15	0.2862	6.0832	0.0001	7.26272	.0001
9	RADDIST	25%	-0.12557	0.0425	1.30	0.1719	7.2126	0.0001	7.48951	.0001
10	RADDIST	50%	-0.13593	0.0334	1.42	0.1149	12.4433	0.0004	7.80335	.0001
11	MRPDIST	5%	-0.10236	0.0766	1.35	0.0890	3.6919	0.0001	5.06057	.0001
12	MRPDIST	10%	-0.11067	0.0614	1.05	0.3942	6.3971	0.0001	6.31412	.0001
13	MRPDIST	20%	-0.1064	0.0818	1.21	0.2342	10.1846	0.0001	6.98284	.0001
14	MRPDIST	25%	-0.10505	0.0939	1.20	0.2399	11.0365	0.0001	6.94685	.0001
15	MRPDIST	50%	-0.09031	0.1600	1.11	0.3391	26.2156	0.0001	7.31101	.0001

Table 3 Results of Two-Stage Least Squares Analysis, Men Aged 66-70, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped in Quintiles (5 groups). For example, in row 4, the results are for the model including URO_RATE in 4 groups (grouped in quartiles), RADDIST in 5 groups (grouped in quintiles) and MRPDIST in 5 groups (grouped in quintile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.14251	0.0051	1.21	0.2214	10.4508	.0001	9.34480	.0001
2	URO_RATE	10%	-0.12017	0.0598	1.34	0.1633	9.3567	.0001	8.27348	.0001
3	URO_RATE	20%	-0.03094	0.7174	1.50	0.1223	5.7310	.0001	6.57506	.0001
4	URO_RATE	25%	-0.01792	0.8430	1.62	0.0950	4.9035	.0021	6.42072	.0001
5	URO_RATE	50%	-0.04893	0.6084	1.69	0.0964	6.9278	.0085	6.97754	.0001
6	RADDIST	5%	-0.03791	0.6121	1.26	0.1706	3.0356	.0001	3.96423	.0001
7	RADDIST	10%	-0.01943	0.8050	1.26	0.2143	5.0141	.0001	5.50306	.0001
8	RADDIST	20%	-0.03094	0.7174	1.50	0.1223	7.6359	.0001	6.57506	.0001
9	RADDIST	25%	-0.03521	0.6785	1.91	0.0390	10.4970	.0001	7.26019	.0001
10	RADDIST	50%	-0.03374	0.7237	2.37	0.0153	14.8658	.0001	7.01479	.0001
11	MRPDIST	5%	-0.01321	0.8640	1.51	0.0545	3.2129	.0001	4.06973	.0001
12	MRPDIST	10%	-0.03593	0.6587	1.20	0.2626	5.1025	.0001	5.44187	.0001
13	MRPDIST	20%	-0.03094	0.7174	1.50	0.1223	8.1697	.0001	6.57506	.0001
14	MRPDIST	25%	-0.03179	0.7165	1.50	0.1322	9.6597	.0001	6.83481	.0001
15	MRPDIST	50%	-0.00877	0.9238	1.37	0.2032	22.8643	.0001	7.67112	.0001

Table 4 Results of Two-Stage Least Squares Analysis, Men Aged 66-70, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped in Quartiles (4 groups). For example, in row 5, the results are for the model including URO_RATE in 2 groups (grouped at the median), RADDIST in 4 groups (grouped in quartiles) and MRPDIST in 4 groups (grouped in quartiles).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.14509	0.0054	1.39	0.1123	10.4062	.0001	9.69162	.0001
2	URO_RATE	10%	-0.12211	0.0671	1.60	0.0699	9.1658	.0001	8.57940	.0001
3	URO_RATE	20%	-0.03838	0.6643	1.92	0.0445	6.9230	.0001	7.35564	.0001
4	URO_RATE	25%	-0.01595	0.8652	2.05	0.0374	6.5716	.0002	7.28139	.0001
5	URO_RATE	50%	-0.07162	0.4840	2.28	0.0338	8.6103	.0034	7.76668	.0001
6	RADDIST	5%	-0.01595	0.8434	1.22	0.2145	2.8577	.0001	3.70156	.0001
7	RADDIST	10%	0.003904	0.9630	1.22	0.2505	5.0032	.0001	5.49616	.0001
8	RADDIST	20%	-0.01247	0.8917	1.61	0.1060	7.9518	.0001	6.91761	.0001
9	RADDIST	25%	-0.01595	0.8652	2.05	0.0374	9.3927	.0001	7.28139	.0001
10	RADDIST	50%	0.015247	0.8857	2.62	0.0153	14.7115	.0001	7.42903	.0001
11	MRPDIST	5%	-0.01351	0.8664	1.74	0.0189	3.0740	.0001	4.08875	.0001
12	MRPDIST	10%	-0.02989	0.7317	1.48	0.1153	4.3921	.0001	5.41918	.0001
13	MRPDIST	20%	-0.0201	0.8259	2.02	0.0329	7.1438	.0001	6.92919	.0001
14	MRPDIST	25%	-0.01595	0.8652	2.05	0.0374	8.2774	.0001	7.28139	.0001
15	MRPDIST	50%	-0.00242	0.9802	1.91	0.0759	20.6398	.0001	8.76102	.0001

Table 5 Results of Two-Stage Least Squares Analysis, Men Aged 66-70, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped at the Median (2 groups). For example, in row 1, the results are for the model including URO_RATE in 20 groups (grouped every 5th percentile), RADDIST in 2 groups (grouped at the median) and MRPDIST in 2 groups (grouped at the median).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.14525	0.0065	1.39	0.1307	10.9141	.0001	11.3056	.0001
2	URO_RATE	10%	-0.11435	0.0998	1.64	0.0882	9.9926	.0001	10.7714	.0001
3	URO_RATE	20%	-0.00066	0.9947	2.28	0.0441	7.2359	.0001	9.5439	.0001
4	URO_RATE	25%	0.019561	0.8555	2.74	0.0271	7.5047	.0001	10.1623	.0001
5	URO_RATE	50%	-0.04431	0.7233	4.34	0.0131	8.2419	.0041	12.1629	.0001
6	RADDIST	5%	-0.02041	0.8194	1.18	0.2646	2.7265	.0001	3.6134	.0001
7	RADDIST	10%	0.000863	0.9927	1.16	0.3126	4.7430	.0001	5.9898	.0001
8	RADDIST	20%	-0.04452	0.6703	1.67	0.1375	7.2943	.0001	8.7250	.0001
9	RADDIST	25%	-0.05994	0.5894	2.21	0.0650	7.6913	.0001	9.2458	.0001
10	RADDIST	50%	-0.04431	0.7233	4.34	0.0131	13.3595	.0003	12.1629	.0001
11	MRPDIST	5%	-0.02323	0.8028	2.00	0.0084	3.0224	.0001	3.7013	.0001
12	MRPDIST	10%	-0.06006	0.5737	1.84	0.0559	3.9738	.0001	5.0033	.0001
13	MRPDIST	20%	-0.05626	0.6247	3.12	0.0081	6.2147	.0001	7.1823	.0001
14	MRPDIST	25%	-0.0508	0.6704	3.37	0.0092	7.2760	.0001	8.0115	.0001
15	MRPDIST	50%	-0.04431	0.7233	4.34	0.0131	18.2631	.0001	12.1629	.0001

Appendix 6. Detailed Instrumental Variables Analyses Tables For All Possible Combinations of Levels of Instrumental Variables, Men Aged 71-75, Analyses of the Effect of Radical Prostatectomy Vs. Radiation Treatment.

Table 1 Results of Two-Stage Least Squares Analysis, Men Aged 71-75, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped at the 5th Percentile (20 groups). For example, in row 2, the results are for the model including URO_RATE in 10 groups (grouped in deciles), RADDIST in 20 groups (grouped every 5th percentile) and MRPDIST in 20 groups (grouped every 5th percentile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.08582	0.0644	1.07	0.3496	15.6756	0.0001	7.3661	.0001
2	URO_RATE	10%	-0.12418	0.0248	1.20	0.1800	15.4293	0.0001	5.9200	.0001
3	URO_RATE	20%	-0.10384	0.1816	1.17	0.2246	3.2686	0.0110	3.3342	.0001
4	URO_RATE	25%	-0.10799	0.1452	1.14	0.2625	8.5663	0.0001	3.7719	.0001
5	URO_RATE	50%	-0.11203	0.1595	1.20	0.1933	7.0060	0.0081	3.4451	.0001
6	RADDIST	5%	-0.08582	0.0644	1.07	0.3496	1.9315	0.0103	7.3661	.0001
7	RADDIST	10%	-0.09874	0.0363	0.98	0.5053	2.4910	0.0077	8.6778	.0001
8	RADDIST	20%	-0.09809	0.0427	0.97	0.5251	1.1347	0.3381	9.3684	.0001
9	RADDIST	25%	-0.09534	0.0497	1.08	0.3377	0.7119	0.5447	9.5654	.0001
10	RADDIST	50%	-0.0909	0.0617	1.02	0.4359	1.3551	0.2444	10.1234	.0001
11	MRPDIST	5%	-0.08582	0.0644	1.07	0.3496	4.1888	0.0001	7.3661	.0001
12	MRPDIST	10%	-0.0833	0.0772	1.10	0.3089	6.9544	0.0001	8.4945	.0001
13	MRPDIST	20%	-0.09076	0.0548	1.09	0.3243	13.3668	0.0001	9.3338	.0001
14	MRPDIST	25%	-0.06629	0.1730	1.10	0.3116	11.4962	0.0001	9.0511	.0001
15	MRPDIST	50%	-0.06795	0.1771	1.14	0.2673	12.2770	0.0005	8.9076	.0001

Table 2 Results of Two-Stage Least Squares Analysis, Men Aged 71-75, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped in Deciles (10 groups). For example, in row 3, the results are for the model including URO_RATE in 5 groups (grouped in quintiles), RADDIST in 10 groups (grouped in deciles) and MRPDIST in 10 groups (grouped in deciles).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.09662	0.0440	0.95	0.5478	16.5963	0.0001	10.4141	.0001
2	URO_RATE	10%	-0.1498	0.0102	1.08	0.3529	16.8781	0.0001	8.8006	.0001
3	URO_RATE	20%	-0.16398	0.0761	0.94	0.5318	3.4970	0.0074	4.2568	.0001
4	URO_RATE	25%	-0.14684	0.0819	0.89	0.5935	10.5950	0.0001	5.3702	.0001
5	URO_RATE	50%	-0.18138	0.0558	0.95	0.5127	9.7090	0.0018	4.7277	.0001
6	RADDIST	5%	-0.12796	0.0242	1.25	0.1491	1.9742	0.0082	6.8991	.0001
7	RADDIST	10%	-0.1498	0.0102	1.08	0.3529	2.5550	0.0063	8.8006	.0001
8	RADDIST	20%	-0.15819	0.0090	0.89	0.6047	1.6868	0.1500	10.1057	.0001
9	RADDIST	25%	-0.15141	0.0127	1.22	0.2267	1.7663	0.1513	10.5379	.0001
10	RADDIST	50%	-0.141	0.0205	1.04	0.4145	4.2060	0.0403	11.6496	.0001
11	MRPDIST	5%	-0.14568	0.0103	1.10	0.3219	4.7300	0.0001	7.1052	.0001
12	MRPDIST	10%	-0.1498	0.0102	1.08	0.3529	7.8792	0.0001	8.8006	.0001
13	MRPDIST	20%	-0.15919	0.0069	1.11	0.3257	14.6835	0.0001	10.2050	.0001
14	MRPDIST	25%	-0.1226	0.0467	1.13	0.3073	12.9255	0.0001	9.7182	.0001
15	MRPDIST	50%	-0.12905	0.0470	1.21	0.2448	18.3710	0.0001	9.6432	.0001

Table 3 Results of Two-Stage Least Squares Analysis, Men Aged 71-75, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped in Quintiles (5 groups). For example, in row 4, the results are for the model including URO_RATE in 4 groups (grouped in quartiles), RADDIST in 5 groups (grouped in quintiles) and MRPDIST in 5 groups (grouped in quintile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.10269	0.0376	0.84	0.6817	16.9577	0.0001	13.4840	.0001
2	URO_RATE	10%	-0.16942	0.0058	0.91	0.5618	17.2167	0.0001	12.1420	.0001
3	URO_RATE	20%	-0.2171	0.0425	0.53	0.8869	4.1690	0.0023	5.5941	.0001
4	URO_RATE	25%	-0.18016	0.0607	0.45	0.9213	10.8160	0.0001	7.5480	.0001
5	URO_RATE	50%	-0.23642	0.0342	0.43	0.9034	11.6038	0.0007	6.8935	.0001
6	RADDIST	5%	-0.11284	0.1869	1.21	0.2188	2.8693	0.0001	4.0192	.0001
7	RADDIST	10%	-0.18603	0.0490	0.96	0.4952	3.6715	0.0001	5.0482	.0001
8	RADDIST	20%	-0.2171	0.0425	0.53	0.8869	3.6150	0.0060	5.5941	.0001
9	RADDIST	25%	-0.16415	0.1387	1.08	0.3770	3.1146	0.0251	5.6346	.0001
10	RADDIST	50%	-0.13412	0.2369	0.60	0.7800	6.5145	0.0107	6.5716	.0001
11	MRPDIST	5%	-0.18284	0.0507	0.99	0.4710	3.9646	0.0001	3.6400	.0001
12	MRPDIST	10%	-0.18994	0.0677	0.61	0.8685	5.8613	0.0001	4.4241	.0001
13	MRPDIST	20%	-0.2171	0.0425	0.53	0.8869	10.8082	0.0001	5.5941	.0001
14	MRPDIST	25%	-0.16527	0.1463	0.68	0.7401	11.6589	0.0001	5.3498	.0001
15	MRPDIST	50%	-0.20985	0.1104	0.47	0.8788	20.4834	0.0001	4.9233	.0001

Table 4 Results of Two-Stage Least Squares Analysis, Men Aged 71-75, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped in Quartiles (4 groups). For example, in row 5, the results are for the model including URO_RATE in 2 groups (grouped at the median), RADDIST in 4 groups (grouped in quartiles) and MRPDIST in 4 groups (grouped in quartiles).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.07914	0.1200	1.09	0.3552	16.4821	0.0001	13.8457	.0001
2	URO_RATE	10%	-0.12814	0.0447	1.40	0.1460	16.6660	0.0001	12.6835	.0001
3	URO_RATE	20%	-0.08635	0.4624	1.40	0.1802	3.9135	0.0035	5.5145	.0001
4	URO_RATE	25%	-0.10252	0.3085	1.23	0.2738	11.8843	0.0001	8.3632	.0001
5	URO_RATE	50%	-0.108	0.3790	1.64	0.1305	10.9442	0.0009	7.2036	.0001
6	RADDIST	5%	-0.07448	0.3710	1.29	0.1622	2.4938	0.0004	4.6131	.0001
7	RADDIST	10%	-0.12527	0.1646	1.00	0.4500	3.1370	0.0009	6.2655	.0001
8	RADDIST	20%	-0.1506	0.1247	0.48	0.8871	3.4179	0.0085	7.9327	.0001
9	RADDIST	25%	-0.10252	0.3085	1.23	0.2738	3.2144	0.0219	8.3632	.0001
10	RADDIST	50%	-0.07811	0.4419	0.37	0.9002	8.4828	0.0036	10.5881	.0001
11	MRPDIST	5%	-0.1419	0.1064	1.13	0.3110	2.8376	0.0001	4.4938	.0001
12	MRPDIST	10%	-0.12466	0.1852	0.94	0.5113	4.0978	0.0001	6.1576	.0001
13	MRPDIST	20%	-0.14587	0.1397	0.97	0.4668	6.2001	0.0001	7.8192	.0001
14	MRPDIST	25%	-0.10252	0.3085	1.23	0.2738	7.2974	0.0001	8.3632	.0001
15	MRPDIST	50%	-0.11615	0.2740	1.07	0.3805	14.2177	0.0002	9.6498	.0001

Table 5 Results of Two-Stage Least Squares Analysis, Men Aged 71-75, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped at the Median (2 groups). For example, in row 1, the results are for the model including URO_RATE in 20 groups (grouped every 5th percentile), RADDIST in 2 groups (grouped at the median) and MRPDIST in 2 groups (grouped at the median).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.06694	0.2038	0.76	0.7404	16.2824	0.0001	15.7929	.0001
2	URO_RATE	10%	-0.11843	0.0786	0.96	0.4752	16.3501	0.0001	15.5035	.0001
3	URO_RATE	20%	-0.10948	0.4271	0.44	0.8219	4.2430	0.0020	6.6547	.0001
4	URO_RATE	25%	-0.08579	0.4229	0.08	0.9885	14.5278	0.0001	13.3269	.0001
5	URO_RATE	50%	-0.11611	0.4235	0.11	0.8976	13.0913	0.0003	12.0148	.0001
6	RADDIST	5%	-0.09821	0.3403	1.47	0.0849	2.3072	0.0013	3.5895	.0001
7	RADDIST	10%	-0.1961	0.1087	1.22	0.2690	2.3229	0.0132	4.6468	.0001
8	RADDIST	20%	-0.22203	0.1052	0.33	0.8953	2.6721	0.0304	6.8122	.0001
9	RADDIST	25%	-0.15892	0.2694	1.55	0.1852	2.1682	0.0896	7.3350	.0001
10	RADDIST	50%	-0.11611	0.4235	0.11	0.8976	5.8678	0.0154	12.0148	.0001
11	MRPDIST	5%	-0.14849	0.1461	1.15	0.2970	3.4466	0.0001	4.0519	.0001
12	MRPDIST	10%	-0.1252	0.2699	0.72	0.6894	5.1576	0.0001	5.9033	.0001
13	MRPDIST	20%	-0.15372	0.1958	0.54	0.7482	9.0260	0.0001	8.9790	.0001
14	MRPDIST	25%	-0.08555	0.4908	0.55	0.7004	10.5428	0.0001	9.8778	.0001
15	MRPDIST	50%	-0.11611	0.4235	0.11	0.8976	18.3141	0.0001	12.0148	.0001

Appendix 7. Detailed Instrumental Variables Analyses Tables For All Possible Combinations of Levels of Instrumental Variables, Men Aged 71-75, Analyses of the Effect of Radical Prostatectomy Vs. Radiation Treatment.

Table 1 Results of Two-Stage Least Squares Analysis, Men Aged 76-80, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped at the 5th Percentile (20 groups). For example, in row 2, the results are for the model including URO_RATE in 10 groups (grouped in deciles), RADDIST in 20 groups (grouped every 5th percentile) and MRPDIST in 20 groups (grouped every 5th percentile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.23764	0.0039	1.13	0.2460	13.0494	0.0001	5.28705	.0001
2	URO_RATE	10%	-0.30093	0.0059	1.11	0.2848	10.3294	0.0001	3.41097	.0001
3	URO_RATE	20%	-0.149	0.3480	1.09	0.3336	3.5339	0.0070	1.75222	.0030
4	URO_RATE	25%	-0.22879	0.1090	1.12	0.2817	10.2333	0.0001	2.25535	.0001
5	URO_RATE	50%	-0.12231	0.4625	1.10	0.3191	8.0710	0.0045	1.72764	.0051
6	RADDIST	5%	-0.23764	0.0039	1.13	0.2460	1.0216	0.4308	5.28705	.0001
7	RADDIST	10%	-0.26501	0.0016	1.08	0.3329	1.1797	0.3033	6.26047	.0001
8	RADDIST	20%	-0.25575	0.0024	0.97	0.5139	2.0935	0.0791	7.07381	.0001
9	RADDIST	25%	-0.24832	0.0035	1.11	0.3003	1.1271	0.3367	7.12412	.0001
10	RADDIST	50%	-0.25672	0.0025	0.93	0.5737	3.0039	0.0832	7.54839	.0001
11	MRPDIST	5%	-0.23764	0.0039	1.13	0.2460	1.4448	0.1115	5.28705	.0001
12	MRPDIST	10%	-0.24319	0.0035	1.19	0.1958	2.1433	0.0289	6.15573	.0001
13	MRPDIST	20%	-0.25147	0.0028	1.16	0.2372	3.2325	0.0117	6.69230	.0001
14	MRPDIST	25%	-0.24959	0.0036	1.14	0.2630	1.1731	0.3185	6.60099	.0001
15	MRPDIST	50%	-0.25509	0.0030	1.17	0.2315	2.5604	0.1097	6.95313	.0001

Table 2 Results of Two-Stage Least Squares Analysis, Men Aged 76-80, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped in Deciles (10 groups). For example, in row 3, the results are for the model including URO_RATE in 5 groups (grouped in quintiles), RADDIST in 10 groups (grouped in deciles) and MRPDIST in 10 groups (grouped in deciles).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.26883	0.0015	1.12	0.2927	13.0700	0.0001	7.59549	.0001
2	URO_RATE	10%	-0.36005	0.0018	1.07	0.3722	10.4161	0.0001	5.15012	.0001
3	URO_RATE	20%	-0.28514	0.1109	1.05	0.3985	3.5465	0.0068	2.54280	.0001
4	URO_RATE	25%	-0.31253	0.0462	1.15	0.2917	10.2978	0.0001	3.51654	.0001
5	URO_RATE	50%	-0.26934	0.1527	1.16	0.2933	8.8066	0.0030	2.66608	.0002
6	RADDIST	5%	-0.3225	0.0039	1.18	0.2210	1.4206	0.1110	4.02975	.0001
7	RADDIST	10%	-0.36005	0.0018	1.07	0.3722	2.0406	0.0315	5.15012	.0001
8	RADDIST	20%	-0.35683	0.0026	1.01	0.4433	2.8199	0.0238	6.03521	.0001
9	RADDIST	25%	-0.3266	0.0064	1.26	0.2001	2.5476	0.0542	6.15020	.0001
10	RADDIST	50%	-0.34329	0.0043	1.01	0.4418	7.2009	0.0073	6.81224	.0001
11	MRPDIST	5%	-0.33906	0.0027	1.03	0.4205	1.5861	0.0642	4.09019	.0001
12	MRPDIST	10%	-0.36005	0.0018	1.07	0.3722	2.5141	0.0101	5.15012	.0001
13	MRPDIST	20%	-0.36952	0.0015	1.02	0.4392	4.5931	0.0011	6.01116	.0001
14	MRPDIST	25%	-0.38242	0.0017	0.97	0.4943	2.4603	0.0609	5.75650	.0001
15	MRPDIST	50%	-0.39824	0.0012	1.00	0.4585	5.6657	0.0174	6.27273	.0001

Table 3 Results of Two-Stage Least Squares Analysis, Men Aged 76-80, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped in Quintiles (5 groups). For example, in row 4, the results are for the model including URO_RATE in 4 groups (grouped in quartiles), RADDIST in 5 groups (grouped in quintiles) and MRPDIST in 5 groups (grouped in quintile).

Obs	IV_NAME	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	-0.26495	0.0021	1.08	0.3554	13.3146	0.0001	10.1796	.0001
2	URO_RATE	10%	-0.36356	0.0024	1.00	0.4516	10.4174	0.0001	7.2921	.0001
3	URO_RATE	20%	-0.31458	0.1104	0.94	0.4994	3.6946	0.0053	3.6904	.0001
4	URO_RATE	25%	-0.3142	0.0588	1.16	0.3140	10.9717	0.0001	5.6912	.0001
5	URO_RATE	50%	-0.30176	0.1512	1.15	0.3267	9.2710	0.0023	4.3060	.0001
6	RADDIST	5%	-0.19891	0.2302	1.11	0.3246	1.7739	0.0229	2.3622	.0001
7	RADDIST	10%	-0.3205	0.0768	0.99	0.4604	2.5624	0.0062	3.0912	.0001
8	RADDIST	20%	-0.31458	0.1104	0.94	0.4994	3.7065	0.0051	3.6904	.0001
9	RADDIST	25%	-0.22523	0.2677	1.31	0.2197	3.8319	0.0094	3.7211	.0001
10	RADDIST	50%	-0.29179	0.1624	0.91	0.5042	9.7457	0.0018	4.3539	.0001
11	MRPDIST	5%	-0.23008	0.2131	0.86	0.6526	1.4163	0.1240	2.0610	.0018
12	MRPDIST	10%	-0.27913	0.1474	0.96	0.4958	2.3888	0.0145	2.8720	.0001
13	MRPDIST	20%	-0.31458	0.1104	0.94	0.4994	4.3558	0.0016	3.6904	.0001
14	MRPDIST	25%	-0.31812	0.1475	0.77	0.6607	2.9289	0.0324	3.2348	.0002
15	MRPDIST	50%	-0.38123	0.0944	0.65	0.7337	6.8239	0.0090	3.7356	.0001

Table 4 Results of Two-Stage Least Squares Analysis, Men Aged 76-80, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped in Quartiles (4 groups). For example, in row 5, the results are for the model including URO_RATE in 2 groups (grouped at the median), RADDIST in 4 groups (grouped in quartiles) and MRPDIST in 4 groups (grouped in quartiles).

Obs	IV_NAME	LINK	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	1	-0.25308	0.0042	1.18	0.2541	13.1170	0.0001	10.4396	.0001
2	URO_RATE	10%	2	-0.33909	0.0072	1.14	0.3155	10.2232	0.0001	7.4094	.0001
3	URO_RATE	20%	3	-0.19826	0.3803	1.03	0.4147	3.5576	0.0067	3.2925	.0003
4	URO_RATE	25%	4	-0.24383	0.1666	1.34	0.2174	11.9995	0.0001	6.0922	.0001
5	URO_RATE	50%	5	-0.15105	0.5411	1.28	0.2605	8.7325	0.0031	3.9160	.0003
6	RADDIST	5%	1	-0.25688	0.0931	1.16	0.2735	1.5307	0.0701	3.0429	.0001
7	RADDIST	10%	2	-0.34064	0.0394	1.07	0.3836	2.0191	0.0336	4.2428	.0001
8	RADDIST	20%	3	-0.31741	0.0680	1.00	0.4340	2.9278	0.0198	5.7161	.0001
9	RADDIST	25%	4	-0.24383	0.1666	1.34	0.2174	3.1333	0.0246	6.0922	.0001
10	RADDIST	50%	5	-0.26318	0.1368	1.21	0.2987	9.2014	0.0024	7.8082	.0001
11	MRPDIST	5%	1	-0.21562	0.1868	1.11	0.3297	0.8559	0.6214	2.8881	.0001
12	MRPDIST	10%	2	-0.2314	0.1690	1.44	0.1346	1.2700	0.2544	4.2910	.0001
13	MRPDIST	20%	3	-0.2502	0.1393	1.60	0.1086	2.4132	0.0469	5.9623	.0001
14	MRPDIST	25%	4	-0.24383	0.1666	1.34	0.2174	1.6398	0.1780	6.0922	.0001
15	MRPDIST	50%	5	-0.25399	0.1537	1.43	0.2005	3.9156	0.0479	7.6918	.0001

Table 5 Results of Two-Stage Least Squares Analysis, Men Aged 76-80, with Three Instrumental Variables (URO_RATE, RADDIST, and MRPDIST) Controlling for Covariates, Where the Instrumental Variables Not Named in the Row is Grouped at the Median (2 groups). For example, in row 1, the results are for the model including URO_RATE in 20 groups (grouped every 5th percentile), RADDIST in 2 groups (grouped at the median) and MRPDIST in 2 groups (grouped at the median).

Obs	IV_NAME	LINK	LINK	TRT_EST	PROB_T	F_OVERID	P_OVERID	TRT_EQ_F1	TRT_EQ_P1	TRT_EQ_F2	TRT_EQ_P2
1	URO_RATE	5%	1	-0.26483	0.0029	1.12	0.3243	13.3836	0.0001	12.6922	.0001
2	URO_RATE	10%	2	-0.35978	0.0047	1.07	0.3823	10.6555	0.0001	9.9762	.0001
3	URO_RATE	20%	3	-0.31263	0.1875	0.83	0.5264	4.2375	0.0020	5.0779	.0001
4	URO_RATE	25%	4	-0.26409	0.1386	1.49	0.2037	13.3948	0.0001	10.7614	.0001
5	URO_RATE	50%	5	-0.29077	0.2749	1.55	0.2124	10.5286	0.0012	8.0104	.0001
6	RADDIST	5%	1	-0.25015	0.2140	1.15	0.2924	1.3762	0.1323	2.0880	.0031
7	RADDIST	10%	2	-0.43047	0.0643	1.03	0.4128	1.7520	0.0724	2.9779	.0006
8	RADDIST	20%	3	-0.37795	0.1355	0.83	0.5256	2.5512	0.0373	4.5318	.0001
9	RADDIST	25%	4	-0.25283	0.3375	1.42	0.2261	2.4553	0.0613	4.8684	.0002
10	RADDIST	50%	5	-0.29077	0.2749	1.55	0.2124	7.0461	0.0080	8.0104	.0001
11	MRPDIST	5%	1	-0.17681	0.3964	0.82	0.6738	1.4140	0.1251	2.1435	.0034
12	MRPDIST	10%	2	-0.21712	0.3187	1.08	0.3745	2.4472	0.0122	3.5563	.0001
13	MRPDIST	20%	3	-0.26729	0.2307	1.24	0.2892	4.5468	0.0012	5.6977	.0001
14	MRPDIST	25%	4	-0.2176	0.3854	1.14	0.3341	3.6098	0.0128	5.3592	.0001
15	MRPDIST	50%	5	-0.29077	0.2749	1.55	0.2124	8.0688	0.0045	8.0104	.0001

Appendix 8. Abstracts Accepted for the American Urological Association Annual Meeting, May 25-30, 2002.

AGE-SPECIFIC EFFECTS OF COMORBIDITY, GRADE, AND ACCESS ON PROSTATE CANCER TREATMENT CHOICE

Elizabeth A Chrischilles*, John M Brooks, Shane D Scott, Shari S Chen-Hardee, Badrinath R Konety, Iowa City, IA

Introduction and Objectives:

Prostate cancer-specific survival and overall survival are closest in men aged 65-69. We hypothesized that tumor grade, comorbidity, and provider access would have the greatest effect on choice between aggressive and conservative treatment at this age. A relationship is theorized between provider access and treatment choice because of the level of uncertainty associated with treatment at this age.

Methods:

Data were from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Men (n=36,333) were diagnosed with clinically localized prostate cancer during 1986-1995. Aggressive treatment (radiation; radical prostatectomy) and tumor grade (Well, Moderately, and Poorly differentiated for Gleason scores of 2-4, 5-7, and 8-10) were from SEER. Charlson score (higher score = more comorbidity) was based on Medicare hospital claims diagnoses. Access to radical prostatectomy was the distance to the nearest hospital performing radical prostatectomies minus distance to the nearest non-prostatectomy hospital (differential distance).

Results:

Men with advanced age, higher comorbidity and who lived relatively far from a prostatectomy hospital were less likely and men with higher tumor grade were more likely to receive aggressive treatment. Aggressive treatment occurred in 75.4%, 52.9%, and 15.0% of men aged 65-69, 70-84, and 85+, respectively. Effects of tumor grade, comorbidity, and distance to prostatectomy hospital were greatest among men aged 65-69 (Table).

Conclusions:

Comorbidity, tumor grade and access to care influence treatment choice most strongly among men aged 65-69

EFFECTIVENESS OF AGGRESSIVE TREATMENTS FOR EARLY STAGE PROSTATE CANCER: EVIDENCE FROM SEER-MEDICARE USING INSTRUMENTAL VARIABLE ESTIMATION

John M Brooks*, Elizabeth A Chrischilles, Shane D Scott, Shari S Chen-Hardee, Badrinath R Konety, Iowa City, IA

Introduction and Objectives:
With the advent of PSA screening, increasing numbers of men have been diagnosed and treated with radiation therapy or radical prostatectomy (RP) for early-stage prostate cancer (ESPC). While such treatments have proven beneficial for many patients, it is unclear whether they have been over- or underutilized across the population of ESPC patients. Using instrumental variable (IV) methods with retrospective healthcare data, we estimated the survival benefits for ESPC patients on the extensive margin of practice – the benefits available from increasing the rate of aggressive treatment (radiation or RP) for patients with ESPC.

Methods:
Men aged 65 and over who were diagnosed with ESPC during 1986-1995 were identified from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database (n=36,333). Patients were grouped by their access to hospitals performing RP and urologists. IV estimates were obtained by exploiting differences in treatment and survival rates between groups. IV techniques yield average estimates for the subset of patients whose treatment choices were affected by provider access – the "marginal patients". Because these estimates are based on access differences and reflect provider discretion, they provide a natural estimate of survival benefits on the extensive margin.

Results:
Either radiation or RP was used to treat 20,345 (56.0%) men with ESPC in the eight SEER registries. ESPC treatment rates varied with provider access. Based on this variation, we found a significant positive relationship between aggressive treatment and five-year survival. Our estimate suggests that a five percentage point increase in the rate of aggressive treatment would have resulted in a one percentage point increase in the five year survival rate of marginal ESPC patients.

Conclusions:
Results suggest that aggressive treatments (radiation or RP) were underutilized in patients with ESPC during the time period of our study.

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
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REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 1 Apr 03

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession document numbers be changed to "Approved for public release; distribution unlimited." Copies of these reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322 or by e-mail at judy.pawlus@det.amedd.army.mil.

FOR THE COMMANDER:

Phyllis Rinehart

Encl

PHYLLIS M. RINEHART
Deputy Chief of Staff for
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